REVISED VERSION: 8.16.02

SJÖGREN'S SYNDROME: A GUIDE FOR THE PATIENT

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SUMMARY

Sjögren's syndrome is a chronic disorder of unknown cause characterized by a particular form of dry mouth and dry eyes. This loss of tears and saliva may result in characteristic changes in the eyes (called aqueous tear deficiency or keratoconjunctivitis) and in dryness of the mouth (called sicca or xerostomia) with deterioration of the teeth, increased oral infection, difficulty in swallowing, and painful mouth. Thus, dryness of eyes and mouth are termed keratoconjunctivitis sicca (KCS). There are many different causes for KCS. When they occur as a result of an autoimmune process, the condition is called Sjögren's syndrome, which usually occurs in middle-aged women and has prevalence in about 1 in 500 adult persons. There is a marked predisposition of women (about 9:1) with two peaks of age of onset. The first peak occurs during the childbearing period in the mid 30's and a second peak in postmenopausal years during the mid 50's although the condition can occur at virtually any age including in children as part of the spectrum of juvenile rheumatoid arthritis. Patients may also have inflammation of the joints (arthritis), muscles (myositis), nerves (neuropathy), thyroid (thyroiditis), kidneys (nephritis), lungs (pneumonitis), lymph node swelling (lymphadenopathy) or other areas of the body. Also, patients may have severe fatigue and disruption of their sleep pattern. Sjögren's can exist as a primary disorder or can be associated with other autoimmune disorders including rheumatoid arthritis, systemic lupus, polymyositis, scleroderma, autoimmune hepatitis (biliary cirrhosis) and endocrine disorders such as thyroiditis.

Diagnosis is based on clinical examination of the eyes and mouth, including measurement of the flow rate for tears and saliva. The blood of Sjögren's patients may contain antibodies directed against normal cellular substances such as nuclear antigens (i.e. antinuclear antibodies, ANA) including particular nuclear proteins termed Sjögren's associated proteins A and B (SS-A and SS-B), and against a portion of the antibody molecule (i.e.. the Fc portion immunoglobulin IgG which is also present in patients with rheumatoid arthritis and termed the 'rheumatoid factor'). Therefore, this disease is termed an"autoimmune" disorder to denote the apparent reaction of the immune system against the patient's own tissues. In some patients, a biopsy of the minor salivary gland (taken from the inside of the lower lip) help confirm the diagnosis by demonstrating the immune cells within the gland and allows evaluation of the extent of destruction of the glandular elements.

Sjögren's syndrome is not fatal. However, attention must be paid to preventing the complications due to dry mouth (such as rampant caries) and to dry eyes (corneal erosions and infections), as well as prevention and treatment of other organ systems involved as a consequence of the disease. In addition, patients may have severe fatigue and cognitive disorders that limit their daily activities as a result of either

their disease process or resulting interruptions in their sleep pattern. Although this fatigue is often a chief complaint of patients, it is important to recognize that many different processes can cause fatigue and simply giving medications that modulate the immune system may cause side effects without improving the fatigue.

The risk for passing this disease on to family members is extremely low, since multiple different genes play a role in predisposition to disease development. There is a slightly increased incidence of autoimmune diseases in siblings and children. It is likely that some environmental agent (such as a virus) triggers the disease process in individuals when other predisposing genes are present. Pregnant women with Sjögren's syndrome should notify their obstetricians and pediatricians, since maternal autoantibodies may cross the placenta and cause problems for the infant.

The goal of this article is not to make patients into physicians. It is to allow patients to identify certain symptoms, laboratory tests and therapies that may be relevant to their case. We have used technical terms since these may facilitate discussions with your physician and dentists. Also, the technical terms will help in searching the Internet (particularly the National Library of Medicine called PubMed) for relevant publications and to locate research centers near your home. Also, this article does not intend to replace information from other sources including the Sjögren's Syndrome Foundation (www.ssf.org) or the Arthritis Foundation. It tries to present more technical information as a point for discussion with your rheumatologists and dentists.

II. Historical Background

Historically, Mikulicz first reported these symptoms in 1898 so this condition initially was called "Mikulicz syndrome." However, the term Mikulicz syndrome was also applied to many other causes of dryness including tuberculosis and lymphoma (a lymphoid tumor) of the glands. Thus, the term "Mikulicz" syndrome lost specificity in terms of predicting prognosis or response to therapy and is no longer used. Currently, the condition is named for Henrik Sjögren (pronounced sho-gren), a Swedish ophthalmologist, who reported the association of severe dry eyes (1), dry mouth and rheumatoid arthritis in 1933. Later, it was recognized that patients might have dry eyes and dry mouth but no rheumatoid arthritis. Thus, the distinction was made as primary Sjögren's syndrome (1° SS) with no associated rheumatoid arthritis or systemic lupus) and secondary Sjögren's syndrome (2° SS), where SS was associated rheumatoid arthritis or other well defined autoimmune disorder such as systemic lupus erythematosus, or scleroderma. 1° SS and 2° SS both occur predominantly in middle-aged women, although they may be present in either sex at any age.

Until recently, there has been no internationally accepted criteria for diagnosis of Sjögren's syndrome. In fact, very different criteria were used by different physicians. Although the diagnostic tests for dry eyes are well standardized, the definition for the "oral" component of Sjögren's syndrome remained controversial (2). This has resulted in confusion in the medical literature and in clinical practice. We favor a stringent criteria for diagnosis of Sjögren's syndrome in order to identify a group of patients with objective evidence of keratoconjunctivitis sicca and a systemic autoimmune process. Using the San Diego criteria, the frequency of primary SS is about 0.5% of adult women. In 1993, the European Economic Community (EEC) proposed an initial "working" classification that was less stringent in the features required for diagnosis. The frequency of patients filled the EEC preliminary criteria was about 10 fold higher than those fulfilling the San Diego criteria. Virtually all patients who fulfilled the San Diego criteria also fulfill the EEC criteria, but the converse is not true. Therefore, a patient might be diagnosed with SS based on the EEC criteria by one rheumatologist but told that they do not have SS by a different rheumatologist who uses the San Diego diagnosis. This discrepancy reflects an honest difference of opinion among rheumatologists who use different criteria for diagnosis. Fortunately, a new international criteria has been adopted and using the new criteria (which requires either a characteristic minor salivary gland biopsy or an autoantibody to SS-A or SS-B), the frequency of SS is about 0.5% (the new criteria are listed in Table 1).

The goals of a diagnostic criteria are to help guide therapy and predict future complications. Regardless of the cause or whether a patient is diagnosed with SS, the oral and ocular symptoms of dryness deserve treatment. However, the key issue is whether "topical" treatment of dry eyes and dry mouth is sufficient, or whether there is an active autoimmune process, which also requires therapy. Also, a stringent criteria will allow physicians to look for other causes of dryness. Other conditions that can mimic Sjögren's syndrome are hepatitis virus, retroviral (HIV or HTLV) viral infection, medications with drying side effects, depression, sarcoidosis, autonomic neuropathy (often associated with multiple sclerosis or diabetes), and tumors that can infiltrate the lacrimal or salivary glands. Also, low-grade infections termed blepharitis or oral yeast infections (described below) may cause symptoms of painful eyes and mouth and respond to an entirely different form of therapy.

III. THE OCULAR AND ORAL SYMPTOMS OF SJÖGREN'S SYNDROME

When patients complain of dryness, they are describing increased friction as the eyelid traverses the ocular globe or the tongue moves over the bucal mucosa (3). The tear and saliva film allow a "blanket of lubrication" that permits decreased friction necessary for actions such as blinking (4, 5), talking or swallowing (6). The

low friction movement of both ocular and oral mucosal surfaces also is facilitated by the cells lining these mucosal surfaces., These cells contain mucins that are actually anchored within the membrane of the cells that line the ocular and oral surfaces. An analogy would be that the mucins on the cell surface and in the tear/saliva film serve as "ball bearings" that facilitate a low-friction gliding motion (7) (8, 9). Thus, the production of mucins and water to form stable "films" is an initial goal of therapy. Also, the restoration of the mucins on the lining mucosal cells is important for efficient relief of symptoms in patients with Sjögren's syndrome.

However, tears and saliva are much more than "water". In addition to water, they contain a wide variety of proteins (including anti-bacterial factors and growth factors), oligosaccharides (small sugar molecules that have anti-bacterial properties), mucins (small oil molecules that together with water facilitate lubrication), nutrients (including glucose and amino acids) and hormones (including insulin and growth hormone) (10-12). Thus the tear and saliva films also supply the factors necessary for prevention of infection or deterioration of the mucosal surfaces.

The perception of dry eyes or dry mouth in SS represents part of a functional unit (Figure 1) (3). The ocular surface is heavily innervated by unmyelinated sensory nerves that go from the peripheral nerve endings toward the brain (e.g. termed afferent nerves), and eventually end in an area of the midbrain called the lacrimatory nucleus (13). In a similar manner, afferent nerves from the buccal mucosa travel to an adjacent area in the midbrain called the salivatory nucleus. Both the lacrimatory and salivatory nuclei of the midbrain also receive inputs from higher cortical centers (Figure 1). The important role of the cortical centers in the control of salivation and lacrimation is evident in clinical practice by certain "centrally acting" medications (such as clonidine for blood pressure) or antidepressant medications (such as tricyclic drugs) induces symptoms of dryness as a side effect to their beneficial action on central nervous system (14, 15). The "reversible dryness" which goes away when the medications are stopped. This is an example of how dryness can occur reversibly with functionally intact lacrimal and salivary glands. The action of medications on the brain to control saliva is just an extension of the original historic studies for the role for cortical function in stimulated salivary flow by Pavlov who measured increased salivation in dogs conditioned to respond to sound and smell (16). Literature is filled with quotes that the heroine developed a dry mouth and dry eyes (along with a fluttering heart) in anxious anticipation of some event, again as a result of cortical function influencing the autonomic nervous system.

After the net signal from the afferent peripheral nerves from the mucosal surfaces and the neural input from the higher cortical centers (Figure 1) is "integrated" in the midbrain (ie. lacrimatory and salvatory nuclei) (17). If the decision by the brain is to stimulate saliva or tear flow, two types of neural signals emerge are sent from

the brain (termed efferent neural fibers to designate nerve fibers leaving the brain and going to the periphery). One type of nerve fiber goes to the blood vessels and is called adrenergic since they use adrenaline (also known as epinephrine) or the closely related molecule noradrenalline (also known as norepinephrine) as their neurotransmitter molecule. A second set of nerves goes from the brain to the lacrimal and salivary glands. These latter efferent nerves are termed cholinergic nerves since they use acetylcholine as their neurotransmitter. Cholinergic nerves also use vasoactive intestinal peptide (VIP) and other transmitters such as calcitonin related peptide in addition to acetylcholine as their neurotransmitters (18, 19). Each of these neurotransmitters is potential sites of therapy to not only increase saliva/tears but also to maintain glandular integrity and promote glandular regrowth.

Dry mouth results from decreased salivary gland function. Under normal conditions, a low level of saliva is produced continuously to lubricate the mouth and is called "basal" or "resting" salivary secretion. The volume of resting saliva produced per day by normals can be up to several liters (or quarts) of fluid. When stimulation by taste, chewing, or smell occurs, the level of salivary flow is further increased and is called "stimulated" secretion. In the early stages of Sjögren's syndrome, there is a decrease in the "basal" secretions, so that patients experience maximum dryness between meals and during the night. The increased dryness at night also reflects that the entire autonomic system "down-regulates" in normals and even further decreases in Sjögren's patients. In the early stages, Sjögren's patients are still able to eat dry food without difficulty and cry in response to either emotional or chemical stimuli (such as the smell of onions). As the "dryness" syndrome progresses, more fluid is required to eat and swallow and more stimulation in order to tear. Also, patients may awaken at night with the need for water and find it difficult to speak due to dryness of the mouth.

Most saliva is normally made by the parotid, sublingual and submandibular glands, but minor salivary glands located inside the lips also contribute. The saliva made in the parotid glands enters the mouth by a small opening (called Stensen's duct) adjacent to the upper molars on each side of the cheek. Saliva flow is measured in several ways. Most frequently a patient expectorates into a pre-weighed cup or puts a pre-weighed sponge under the tongue for 5 minutes. Another method is a salivary gland scintigraphy scan, where a special material is injected into the arm and the excretion of this material into the saliva is measured by a technique performed by a radiologist. In some research studies, a plastic suction cup is placed over the opening of the duct that leads from the gland into the mouth.

As a result of decreased saliva, the teeth may undergo a more rapid decay, loss of enamel and result in painful, expensive need for dental repair. In some patients, past dental problems have led to the use of caps or implants (called dental

restorations). The dryness will still lead to deterioration under the restoration leading to further pain and expensive replacement. The reason for increased dental decay in SS patients is the important role of saliva in the mechanical removal of food particles by the tongue and the content in normal saliva of proteins and antibodies that retard infection and dental decay.

Some Sjögren's patients develop swelling of the parotid and submandibular glands. The swelling may be sudden in onset, painful and on only one side (i.e. unilateral). This type of problem raises the possibility of infection and even possible abscess in the gland. It is important that this problem be promptly evaluated and treated, since a parotid abscess can rupture and cause serious life threatening infection. The parotid gland infections seem more common when the patient is dehydrated and opening of the gland may be blocked by dried mucus in the secretions. In particular, this may occur in the post-operative setting when the patient has been not allowed water prior to surgery and may be dehydrated after surgery.

The glands may be intermittently swollen or may remain swollen. The chronic swelling is usually the result of the infiltration of lymphocytes into the parotid or submandibular glands (i.e. the major salivary glands). This swelling is important since if it is persistent and if the local lymph nodes are swollen, then a biopsy may be necessary to rule out a lymphoid tumor (possibly a lymphoma). Another situation is the sudden onset of unilateral swelling of the gland that causes pain and swelling. Persistent or acute swelling of the major glands is evaluated by use of a CAT scan or an MRI scan of the "soft tissues" of the neck. If a MRI of the parotid gland is performed, the radiologist should also perform the additional procedure of a MRI angiogram, which requires only about 5 more minutes of scanning and will allow an accurate assessment of the extent of damage to the ducts of the gland. Another method to evaluate the parotid gland is called sialography in which the radiologist puts a tube into the opening of the duct and forces a oil based dye back into the gland. Although this is frequently done in Europe (especially where MRI scanners are not available), we do not advocate the use of sialgography since the risk of complications is of rupturing a duct (particularly in the setting of an acute infection) can lead to long term problems of irritation in the gland.

IV. Symptoms of joint and muscle pain

Although Sjögren's syndrome characteristically affects the eyes and the mouth, other parts of the body may also be affected. Joint and muscle pain are frequently present. Since patients with Sjögren's syndrome often have positive blood tests for rheumatoid arthritis (i.e. the rheumatoid factor or latex fixation test) and a positive antinuclear antibody (called the ANA and often called the lupus test), some patients are told that they have three different diagnoses (i.e. RA, SLE and Sjögren's) when in fact they simply have Sjögren's syndrome. The distinction between 1^{o}SS and 2^{o}

SS is relatively easy since primary SS patients have joint pain, stiffness and weakness but generally lack the characteristic pattern of joint swelling found in most RA patients. Also, in a patient with rheumatoid arthritis, the joint x-rays will show characteristic changes (called joint erosions) and particular therapies must be used to prevent progressive joint damage. In primary SS, it is uncommon to have the same joints involved as in RA but some patients may have a pattern of joint involvement that is an aggressive form of osteoarthritis (called erosive osteoarthritis) that may require treatments similar to RA.

The distinction between primary SS and SLE in terms of joints/muscles is more difficult. The key point in distinguishing the joint/muscle involvement as either primary SS or SLE is not to label but to choose the therapy that is safest and most likely to be effective. Blood test to measure specific enzymes released from damaged muscle are usually elevated in muscle inflammation (myositis). In some patients the muscle symptoms may actually result from inflammation of the nerve and an electrical testing of the nerve/muscle unit by a neurologist (an electromyogram or EMG) may be required.

V. Upper Respiratory Tract Dryness and Sinusitis

Sinusitis and recurrent sinus infections are very common in Sjögren's patients. It is very common for patients to have significant dryness of the upper airways and a cough due to "post nasal drip". Often, they will complain of "runny nose" which seems paradoxical when their eyes and mouth are dry. In normal individuals, most of the pollutants and inhaled infections are rinsed out by the normal flow of nasal fluids that are subsequently swallowed and are not even detected by the individual. However, in Sjögren's patients, the amount of normal "basal" secretion of nasal fluids appears to be decreased, resulting in accumulation of mucus and crusting of the nasal passages. This inability to wash out the normal viral and bacterial infections (to which we are exposed on a regular basis) leads to increased frequency of post nasal drip of mucus (i.e. sticky yellow) secretions and the associated upper respiratory infections and relapse of symptoms soon after treatment to the next infection. For this reason, it is often helpful to "lavage" the sinuses and use humidification methods (described below) to help remove the dry mucus and aid the body's normal mechanisms for resisting such infections.

VI Problems Involving Skin, Lung, Heart, Kidneys And Other Organs In Sjögren's

Sjögren's patients may have a variety of rashes. As noted above, the differential diagnosis between primary Sjögren's and systemic lupus is often very difficult—since both may have similar symptoms. However, the rashes of primary Sjögren's tend to be slightly different. The most common rash of SLE is the "butterfly" or

malar rash. The most common rashes of Sjögren's are called "hyperglobulenic purpura," which are areas of initial areas of dark blotches (called purpura) on the legs and feet that coalesce into larger rashes. In describing rashes in patients with Sjögren's syndrome, it is important to use the normal guidelines of whether the rash is elevated (called palpable) or flat (non-palpable), symmetric or asymmetric, on the trunk (proximal) or the extremities (distal), itching (pruritic) or non-itching (non-pruritic), discrete lesions (the outside borders of each portion of the rash exists as a discrete "island") or grouped lesion (ie. many or most of the skin rash lesions exhibit direct contact with other rashes), and whether the palms of hands or soles of feet are spared. For example, an asymmetric, discrete, elevated rash on only one arm may be a particular type of vasculitis that has a different treatment than a symmetric, non-elevated rash of on both legs. In comparison, a rash with fluid filled "vesicles" in one portion of the body (such as on the chest) suggests an entirely different diagnosis such as shingles, which has still a different type of therapy. In comparison, rashes on the palms and soles (especially if itching) are more likely a drug reaction. Thus, it is important to remember that not all rashes are due to Sjögren's, since some rashes are due to drug allergies (especially to sulfa drugs) or to infections such as herpetic viruses (i.e. shingles).

The lungs may develop an inflammatory response as a result of attack by the immune system. The most common upper airway and lung problems in patients with Sjögren's syndrome are dry cough. Due to dryness, patients may develop dried (inspissated) secretions of mucus in the major airways. This often occurs after a flu or sinus infection. The persistent cough can become severe and subsequent pneumonia can develop behind this obstruction. This problem often occurs after a patient has been dehydrated, such as in the post operative period when they have restricted fluids. Thus, it is important to keep the sinuses and upper airways well humidified and we advocate "sinus lavage" to prevent this problem. Another cause of cough is the reflux of acid from the stomach into the upper airways, a condition termed "gastro-esophageal reflux" (GERD). Even though there may be relatively few stomach symptoms, GERD is a frequent cause of dry cough in the Sjögren's patient.

A serious type of lung involvement is called interstitial pneumonitis and is associated with symptoms of shortness of breath and may not be easily detected on routine chest radiography. To determine the activity of this process, a high resolution chest CAT scan is used to look for inflammation (alveolitis).

The heart may be involved in several ways. Pericarditis, inflammation around the heart, is less frequent but also may cause shortness of breath. A cardiac echo is used to detect this problem. Also unusual but important is a condition called pulmonary hypertension in which shortness of breath results from increased resistance in the lungs (such as pneumonitis) and resulting increased work for the

heart to pump blood through the lungs. A cardiac echo is also used to assess this problem. Identification of this problem is now important due to the recent development of several new medications for this problem.

The liver is an unusual site for involvement in primary Sjögren's and abnormalities of liver functions should suggest another process. For example, hepatitis C will cause symptoms of dryness and abnormal liver test and abnormal blood tests (such as positive rheumatoid factor or an ANA). Also, many drugs that are used in arthritis patients (including anti-inflammatory agents such as Motrin (ibuprofen), Advil (naproxen), Voltaren (diclofena), Clinoril (sulindac) or methotrexate can cause elevation of liver tests and should be the most immediate suspects. Also, other drugs that are used for pain control or fibromyalgia (such as amytriptline, nortryptyline, flexeril, zanaflex and many others) can cause elevation of liver tests as well as increased dryness. Elevation of liver tests such as the alkaline phosphatase (a measure of increased pressure on the ducts of the liver) could suggest undiagnosed gall bladder disease, pancreatitis, or other autoimmune diseases such as biliary cirrhosis, autoimmune hepatitis or sclerosing cholangitis.

The kidneys may be affected by several different types of processes. The most common cause of decreased kidney function is the use of anti-inflammatory medications including those available over the counter such as Ibuprofen (Motrin), and Advil (naproxen). The kidneys also may be affected by the newer drugs such as Vioxx (Rofecoxib), Celebrex (Celecoxib) and Bextra (valdecox). These medications also may cause elevation in blood pressure and fluid retention due to their effects on the kidney. In general, anti-inflammatory drugs that are taken once daily (such as Vioxx, Bextra or Feldene) cause more fluid retention than drugs that must be taken several times a day (Celebrex, Clinoril, Motrin) since the "half life" of the latter drugs allows the kidney some time away from the drug's side effect.

A more serious and less reversible renal manifestation are interstitial nephritis or glomerulonephritis. Interstitial nephritis involves the tubules in the kidney and may exist in a "latent" form in many SS patients. They will experience no symptoms until exposure to certain toxins or medications may cause the renal function to deteriorate. Interstitial nephritis appears particularly common in Asian patients living in China or Japan. It is possible that Asian patients may be partially exacerbated by the use of herbal medicines, which are increasing used by a variety of other individuals. Although herbs may be well tolerated in "healthy" individuals, they can take "latent" renal disease in a Sjögren's patient and turn it into life threatening renal disease. Also, over the counter pain medications such as Aleve or Advil, as well as prescription anti-arthritis drugs, may cause rapid deterioration of renal function in patients with Sjögren's syndrome with higher frequency than in other individuals. There is no doubt that many medications and herbs may be efficacious, but the safety of these medications must be closely

monitored in the Sjögren's patient (if they must be taken at all). Patients with Sjögren's syndrome may develop glomerulonephritis (a condition in which the kidneys "leak" protein into the urine). However the finding of glomerulonephritis should suggest the presence of SLE or other conditions such as mixed cryoglobulinemia or amyloidosis.

Although it sounds rather frightening that Sjögren's can affect other parts of the body, it is important to recognize that each of these problems is responsive to therapy if detected early and treated adequately. It is equally important to recognize that SS patients are not exempt from other common problems that may occur in these age groups. Thus, it is unfortunately too common that a treatable problem was delayed in diagnosis since the symptom was incorrectly attributed to SS. For example, the same symptoms in any other patient might have been readily diagnosed as a routine pneumonia, gall bladder stone, kidney stone or ectopic pregnancy.

VII. Neurologic Involvement in Sjögren's Syndrome

The frequency and types of neurologic involvement in Sjögren's syndrome have been very controversial. This partly reflects the differences in criteria used to diagnose Sjögren's syndrome. Involvement of the nervous system is divided into "central" that refers to the brain and spinal cord, and "peripheral" that involves nerves that go from the spinal cord to the extremities.

In terms of peripheral neuropathy, there is a higher incidence of pain/numbness in the extremities especially in patients with skin rashes such as hyperglobulemic purpura. Indeed, the prevention of such neuropathy is one of the most important reasons to treat these conditions. Also, areas of the extremities that go either weak or numb require immediate attention since they may result from vasculitis. Another cause of numbness can be the results of a stroke. Similar to the description of skin rashes, the description of areas of neurologic involvement. They may be symmetric (i.e. both sides) or asymmetric. They may involve only sensory or motor plus sensory. They may involve "cranial nerves" which innervate the facial nerves and muscles. When there is a sudden loss of motor and sensory function in one extremity or the onset of numbness/weakness in the facial muscles, then vasculitis needs to be suspected and promptly evaluated. In addition to the autoimmune process, other factors that lead to nerve damage including elevated cholesterol or diminished B12 or thyroid need to be considered, as well as toxic agents including drugs (especially herbal that may contain high levels of heavy metals such as lead or mercury).

In contrast to the peripheral neuropathies, some patients may develop symptoms that suggest a stroke (also known as a cardiovascular accident or CVA). A small percentage of Sjögren's patients have an increased risk of blood clotting (causing either swelling of the leg/arm or stroke) called an anti-cardiolipin syndrome. Any Sjögren's patient with a past stroke needs to be checked for not only anti-cardiolipin antibodies, but also for lupus anti-coagulant, anti-beta2glycoprotein I antibody and homocysteine since each of these factors predispose to stroke or blood clot. There has been a debate about the incidence of multiple sclerosis in Sjögren's patients. Although vasculitis of the central nervous system can occur in Sjögren's patients (and present with symptoms similar to multiple sclerosis), it is a relatively uncommon event. If a brain MRI is considered, they should make sure that it is performed with "contrast" to visualize any vasculity and also include an MRA (which is the MRI equivalent of an angiogram to see if blood is flowing to all sections of the brain). These studies include no more risk and little more time than a simple MRI, but they must be ordered at the time of the original MRI so that the technician allows enough time between patients.

There has also been a debate about whether patients with Sjögren's syndrome have a higher risk of Alzheimer's disease. There is virtually no evidence for this worrisome concept. It is true that patients with Alzheimer's may have significant symptoms of dryness but it is not due to any immune attack on their salivary or lacrimal glands. Similarly, patients with multiple sclerosis or an unusual condition called pure sensory neuropathy may have dryness due to involvement of regions of the brain cortex or brainstem that are involved with salivation and lacrimation. Even though these patients do not have Sjögren's syndrome, they may benefit from the conservative approaches to therapy used for Sjögren's syndrome. In the same line of thought, patients with Sjögren's syndrome benefit from therapies developed originally for other patients who have undergone radiation to the head and neck for cancer.

Viii Fatigue, Fibromyalgia and Depression in SS

Chronic fatigue is defined as at least 6 weeks in duration and usually divided into at least 3 subtypes. First, inflammatory fatigue is due to the release of immune hormones (particularly interleukin-1, IL-1, and interleukin-6, IL-6) and can be diagnosed by blood tests such as elevated sedimentation test (ESR) and c-reactive protein (CRP). A second type of fatigue is due to hormonal abnormalities such as low thyroid, which can have insidious onset in SS patients and may occur in up to 15% of Sjögren's patients. A third and poorly understood form of fatigue is called "chronic fatigue syndrome."

In recent years, there has been a great deal of research into the neurochemistry of depression and chronic fatigue. In some patients, the fatigue is that related to

positional (or orthostatic fatigue) that may be related to hormones produced by the brain (the hypothalmic-adrenal axis). In other patients, they awake feeling as if they have not slept and this type of fatigue is termed "non-restorative" sleep. Patients describe this fatigue as similar to what other and that normal individuals experience when they change time zones after traveling. "Chronic fatigue syndrome" frequently accompanies a condition called fibromyalgia, which is discussed below. These 3 types of pain are not mutually exclusive. The differential diagnosis of fatigue and vague cognitive dysfunction is the most difficult diagnostic challenge for the rheumatologist. Patients are reluctant to being labeled as depressed and want a "medical diagnosis" as a cause for the fatigue. It is important to recognize that each of forms of fatigue (from inflammatory to depression) results from a subtle imbalance in brain's neurochemicals and that the rheumatologist is trying to decide if the problem is due to the immune system or whether another avenue of therapy should be pursued.

What are the common pitfalls in the evaluation of fatigue, perhaps the most troublesome and controversial of symptoms?

A common clinical situation is a patient with fatigue who is referred to the rheumatologist with a low titer of ANA and symptoms of dryness. Although the "normal controls" listed on the bottom of lab tests indicate that an ANA of 1:40 is significant, large studies have shown that such a weak lab test may be present in over 33% of normal individuals (20). The statistical term is that the test is very sensitive but not specific. We generally use a cutoff of ANA 1:320 and even using this higher level, we find that this level is present in 3% of normals. When the frequency of ANA is examined in another statistical method, the risk of developing SS (or SLE) in a patient with an ANA 1:320, the risk is less than 20% (21).. The antibody to SS-A or SS-B has a higher predictive association with developing SS and thus was used for the diagnostic criteria (Table 1). However, there is significant variation in the way this test is run in different labs (22). For example, we are sometimes confronted with a patient with a positive antibody to SS-A but a negative ANA. Since the SS-A molecule is in the cell's nucleus (where it would be part of the nuclear antigens), it is logically impossible for the ANA (containing the SS-A protein) to be negative while the other test for antibody to SS-A to be positive. Thus, one of the tests must be incorrect. The lack of precision of the tests is very upsetting to patients who feel that they have finally arrived at a "hard" diagnosis supported by a lab test to explain their fatigue. Similarly, some patients have undergone a lip biopsy, the gold standard for diagnosis. However, many pathologists are not familiar with the correct methods for reading the biopsy and in a recent study, over 50% of the lip biopsies were re-classified when evaluated by a panel of experts in oral pathology (23).

Back to the basic problem of dryness and fatigue. Many studies have shown that patients with depression (particularly a form of depression called anxious depression) have symptoms of dryness (24-26). Yet when lip biopsies are performed, there is no evidence of inflammation in the gland and the blood tests are also negative for evidence of any immune problem. Thus, it appears that the cause of dryness derives from an imbalance of neural hormones in the brain. Processes in the brain are called “central” while immune processes in the gland are called “peripheral”" Also, patients with decreased memory (early Alzheimer's) also have increased dryness. In these patients, the cause of dryness and decreased memory is the loss of myelinated nerve fibers ina particular region of the brain called the subcortical white matter projections. The problems of diagnosis thus become even more difficult when a patient with fatigue and dryness has positive blood tests or a report of a lip biopsy.

In recent years, the diagnosis of fibromyalgia has stirred a great deal of controversy among both patients and physicians (27, 28). This debate between physicians and patients is unfortunate since it leads to patient as well as physician frustration. Fibromyalgia is characterized by chronic widespread pain (involving all 4 quadrants of the body) and appears to be present in about 5% of the adult population in at least 5 different industrialized countries. The diagnosis is based on detecting 11 of 18 tender points. The etiology of fibromyalgia remains elusive, although there is support for the notion that altered pain processing at the level of number of pain receptors in the skin (i.e. the periphery) and increased sensation of pain processing at the level of the brainstem (i.e. central). The most recent evidence favors the major role at the level of the brain (29). The increased sense of pain and fatigue is increased by stress (30, 31) and associated with increased symptoms of dryness (32). However, the relation to stress does not mean that there is not a neurochemical basis for these symptoms. Recently several studies have suggested that there may be genetic tendencies in these patients (33) including one that may be related to a mutation in a gene that transports serotonin to nerve cells (34). The abnormalities in serotonin are the basis for many of the drugs used to treat depression such as Prozac or Celexa. A similar type of genetic findings had previously been noted in patients with “anxious depression.” Other recent studies also suggest a “central” basis for using a new research tool called a "functional" MRI Brain scan (35). Patients with fibromyalgia were found to have more sensitivity to modest pain stimuli at the trigger point due to increased amplification of the pain signal at the level of the brain stem (a process called “windup.”)

The relationship to stress in fibromyalgia also may have a biochemical basis. Stress involves normally the hypothalamic-pituitary-adrenal (HPA) axis which is best known for the ultimate production of cortisone and adrenaline. As noted above, it has long been known that stress makes the heart rate faster and the mouth dryer. However, multiple other hormones including growth hormone and related factors

are also produced during the stress response by the HPA axis. The hypothalamus (located near the pituitary gland in the brain) receives many types of input from the peripheral nervous system, the hormonal system (including thyroid) and from areas of the brain. One way to evaluate the HPA axis is measurement of growth hormone levels (or its product IgF-1) produced in response to particular stimuli such as injected insulin and these measurements have been reported in fibromyalgia and normal patients. Patients with fibromyalgia had lower production of growth hormone on stimulation (36). The production of growth hormone in response to stress is also strongly related to the same areas of the brain that control areas like salivation and tearing (called cholinergic centers). Once again, the same type of neurochemical abnormalities found in fibromyalgia were found in anxious depression. This is not to minimize or negate fibromyalgia. Rather, it should give hope to fibromyalgia patients that real laboratory abnormalities are being discovered that may respond to new therapies for their fatigue. Also, it suggests that the problem may not be predominantly immune in origin and that attempts to simply give immune modifying drugs should be done with caution since they may do more harm than good. A common question among patients is "The symptoms got better with prednisone (cortisone) so they must be due to immune system. However, it is clear that cortisone is a primary player in the HPA axis and that a response to cortisone does not simply mean that the symptoms are due to an immune problem.

Thus, the most difficult clinical decision in many patients is whether the fatigue and vague cognitive defects are the result of an autoimmune process. It they do result from vasculitis or thrombosis of the central nervous system, then strong chemotherapy drugs must be used. However, if they represent neurochemical imbalance? then an entirely different therapeutic approach involving behavioral modification and perhaps selected drugs that do not increase dryness will be required.

IX. Hereditary Factors In Sjögren's Syndrome

There has been a great deal of research to determine hereditary factors associated with Sjögren's syndrome. To summarize these complicated studies, hereditary factors are important. Particular genes (such as human leukocyte antigen or HLA genes that are used for organ transplantation matching) are inherited in the same manner from parents as are genes for hair color or eye color; that is, one gene from each parent. The HLA genes are important in controlling the immune response and many current research studies are trying to determine exactly how they perform this task. A specific gene named HLA-DR3 is found in high frequency in Caucasian patients with primary Sjögren's syndrome. In different ethnic backgrounds, different HLA genes are associated with Sjögren's. In addition to HLA, at least four other genes are involved. Although the relative frequency of Sjögren's or lupus is

slightly increased in family members of Sjögren's syndrome patients, the specific risk that children or siblings will get these diseases remains very low (<10%). In addition to genetic factors, environmental factors also play a role. It has been proposed that viral infection represents the "other factor," and that Sjögren's syndrome disease results when a genetically susceptible individual (possessing HLA-DR3) is exposed to a certain virus or viruses.

X. Other Causes Of Dry Eyes And Dry Mouth

The production of tears and saliva involves a complicated series of steps. A baseline level of salivation and tear production occurs automatically (just as we breathe and our intestines have motility) without conscious thought about these functions. Thus, the nerves that control these functions are termed the "autonomic" (or "automatic") nervous system. However, additional factors may increase or decrease the signals in tear flow and saliva flow. As Pavlov demonstrated about 100 years ago, dogs can be taught to increase salivation in response to a variety of sounds. Humans start to salivate at the thought or smell of food. Thus, the cognitive areas of the brain can send signals to glands through a series of nerves. Certain drugs can act on the brain to decrease tear and saliva flow and leads to increase symptoms of dryness. One example is tricyclic antidepressants (Elavil or Pamelor) or muscle relaxing agents (such as Flexeril) that influence the metabolism of certain specific brain cells as well as salivary and lacrimal glands. A different class of medications called monoamine oxidase (known as MAO) inhibitors also give severe dryness. Thus, the patient needs to be aware that many drugs, including anti-seizure medications, blood pressure medications, muscle relaxants, and heart medications, lead to increased dryness by affecting different target molecules within the body.

The tear film contains several different components in addition to the "water" part of the tears. Of importance are substances called lipids are made by glands in the eye including the meibomian glands in the eyelids. This lipid stabilizes the tear film and helps retard evaporation. When these lipid-producing glands become inflamed the amount and profile of the types of lipids become altered. The resulting loss of integrity in the outer protective tear film results in the ocular surface becoming inflamed. The inflammation of the eyelids is called "blepharitis." The loss of lipid production (that retards the evaporation of the aqueous tears) will further exacerbate the dry eye symptoms and the appearance of the keratoconjunctivitis sicca.

In addition to problems with the neural activation of the glands, other medical conditions can cause the glands to be dry or to become enlarged (Table 2). The goal of the physical examination and laboratory studies is to determine the precise cause for the dryness and swelling.

XI What Causes Sjögren's Syndrome

The perception of dry eyes or dry mouth in SS represents part of a functional unit (Figure 4) (3). As discussed above (Figure 1), irritation of the ocular surface in Sjögren's patients leads to stimulation of afferent nerves that eventually end in an area of the midbrain called the lacrimatory nucleus (13). In a similar manner, afferent nerves from the buccal mucosa. In Sjögren's syndrome, the characteristic abnormality is the infiltration of lymphocytes into the lacrimal and salivary glands. These lymphocytes release lymphocyte hormones (called cytokines), autoantibodies, and enzymes called metalloproteinases that prevent the gland from adequately responding to the neural signal. Thus the approaches to therapy must be to control the inflammatory response and to help restore the function of the residual glands.

In SS, there is a deficient secretory response of lacrimal and salivary glands in response to the symptoms of dryness (shown schematically in Figure 4)(13). The reasons for this decrease are likely to be multifactorial, but decrease in salivary/lacrimal flow involve both a decrease in the number of secretory units (namely, acini and ducts) and dysfunction of the residual secretory units (37). A normal salivary gland is shown in Figure 4, frame B. The glands that produce saliva exist in “grape-like” clusters. There are no or few lymphocytes in the normal salivary gland. In comparison, shows the presence of lymphocytes in the gland (indicated by the arrows where the glands have been replaced). At higher magnification in Figure 4(frames C and D), the lymphocytes (indicated by arrows) can be seen to attack the glands. These lymphocytic infiltrates are not present in a normal gland (frame B).

Although about half of the secretory units (ie. ducts and acini) are destroyed in the Sjögren's biopsy, there remain about half of the original number of units (38). Thus, a common misconception about SS is that the secretory glands are totally destroyed by cellular mechanisms leading to dryness, a model in which SS is viewed as analogous to insulin deficiency after pancreatic islet cell destruction in type I diabetes (39-42).

This raises the question of why the residual acinar/ductal cells are dysfunctional. It is likely that multiple factors contribute to the diminished function of the residual secretory units. Although the number of nerves in the region of the focal lymphocytic infiltrates are diminished, the residual glandular elements have neural innervation as evidenced by the presence of axons containing synaptophysin and axonal protein 9.5 (43). Thus, factors related to the lymphocytic infiltration and chronic inflammatory responses are preventing function of the neural or the

residual acinar/ductal elements. These factors are likely to include "immune related hormones" (called cytokines such as IL-1 and TNF-a, autoantibodies, and enzymes called metalloproteinases that interfere with cell's ability to interaction (shown schematically in Figure 4).

As a result of the diminished secretion of tears and saliva, the ocular and oral mucosal surfaces undergo a process resembling of a chronic "wound reaction," with further release of proinflammatory cytokines that perpetuate the problem (44, 45). The decreased circulation of tears or saliva prevents the normal removal or inhibition of these proinflammatory cytokines.

Thus, SS provides an interesting overlap of immune, exocrine, and neurochemical processes. Approaches to improved therapy will involve a better understanding of underlying immuno-pathogenesis in order to control the inflammatory response leading to release of cytokines, auto-antibodies and metalloproteinases that inhibit secretory function. In addition, improvement of SS symptoms and perhaps glandular regrowth may be achieved by optimizing the function of the residual secretory units.

XII. Approaches To Treatment

At the present time, no therapies are available to "cure" the underlying causes of Sjögren's syndrome. However, the goals of therapy are to control the underlying inflammatory process (the autoimmune component) and to help the residual glands regain their function or perhaps regenerate. Also, therapies are directed at improving symptoms, preventing the complications (such as dental caries, oral candida, or corneal damage) and preventing disease progression.

A. The Dry Mouth

Clinical management of the dry mouth is a very difficult problem. Some commercial products that may be helpful are listed in Table 4. In addition to chronic dryness, the patients have troublesome intraoral soft tissue problems that include rampant dental caries and difficulty with dentures due to dryness. Painful mouth lesions can result from Candida (yeast) infections of the lips (angular cheilitis) that are more frequent in dry mouth patients. The mouth frequently exhibits macular erythema (redness) on the hard palate and other areas of the oral mucosa. These lesions result from a chronic erythematous form of candidiasis. Before any treatment program is started, it is important to identify contributing factors such as mouth breathing (due to congested nose), heavy smoking, stress, depression, and drugs that have anticholinergic side effects. The most frequently implicated drugs are the phenothiazines, tricyclic antidepressants, antispasmodics, anti-Parkinsonian, and decongestant medications (described in more detail below). Home remedies, some herbal remedies (including Chinese herbs) and

nonprescription medications may possess anticholinergic side effects even though the patients may not recognize these agents as “drugs.”

Dental prophylaxis by their dentists is supplemented by frequent use of dental floss, toothbrush or “Waterpik” device. Several toothpastes and mouth rinses have been developed for the patient with dry mouth. For example, Biotene, “Dental Care,” and Retardent toothpastes are designed for the dry mouth patient (Table 4). These toothpastes lack detergents (such as lauryl sulfate) that are frequently present in many commercial toothpastes and that can irritate dry mucosal membranes. Biotene contains an enzyme important in preventing oral bacterial infections and gingivitis. This enzyme supplement is also present in an oral gel (Oral Balance) that is used to help provide salivary flow at night. “Dental Care” toothpaste contains sodium bicarbonate as a cleaning agent, while Retardent toothpaste uses a chlorine dioxide-based agent to decrease harmful mouth bacteria. These oral products do not contain alcohol as their liquid preservative (such as found in Listerine), which can be drying and irritating. They do not result in staining of tooth enamel which can accompany the use of Peridex. Sugarless chewing gum and sugarless lemon drops are helpful in some cases. Use dental floss where possible. Special toothbrushes are often helpful in cleaning between the teeth. Use only a small amount of toothpaste and start on the biting surfaces, then work down to the gums. However, the field of improved toothpastes is rapidly changing and the web site for several manufactures are listed in Table 4 to help the patient and their dentist keep up with new products.

A variety of saliva substitutes are available (Table 4). These differ in their flavoring agents and preservatives. MouthKote contains a substance called “mucins,” which are glycoproteins that help lubricate the mouth and thus last a little longer than “water-based” lubricants. Salivart spray has the theoretical advantage of containing no preservatives since these agents may be responsible for topical irritation in some patients. After administration of these sprays, parotid flow rates are increased for 7-8 minutes in Sjögren’s patients. However, the patients’ sense of “dry mouth” may be decreased for up to several hours. Although not generally considered as oral lubricants, many patients have found that vaginal lubricants (discussed below) can be applied to the inside of the mouth. There is a much wider and less expensive spectrum of vaginal lubricants available (including at regular grocery and drug stores) than oral lubricants. Although not generally advertised for oral use, the FDA requires oral safety testing for vaginal lubricants and thus the risk of oral side effects is small.

Prevention of dental decay, particularly under caps and crowns is a difficult problem. As patients have discovered, dental reconstruction is expensive and painful. It is even worse when the process begins again under the reconstructed tooth. Treatment with a 0.4% stannous fluoride has been suggested to enhance

dental remineralization of damaged tooth surfaces. Neutral fluoride preparations are often better tolerated than acidic fluoride preparations that are often prescribed by dentists. In patients with severe dental demineralization, special dental "trays" are made for direct application of the fluoride. It is important to use dental specialists and hygienists with experience in dry mouth. Although the dental costs of Sjögren's syndrome should be covered by medical insurance (since it is a complication of a medical condition), most dentists do not want to take the time to bill medical insurance—but it always worth asking. In recent years, a series of varnishes including fluoride and even slow release antibiotics has been helpful.

Increased salivary flow rates have been observed after administration of certain drugs such as pilocarpine or neostigmine as either a mouthwash or as a systemic medication. A commercial preparation of pilocarpine (Salagen) has been approved by the Food and Drug Administration (FDA) for dryness of the mouth in patients with prior radiation therapy and in patients with dry mouth due to Sjögren's. Another drug (Evoxac, cevimeline) was recently approved for dry mouth. Evoxac is chemically similar to the neutransmitter acetylcholine. This medication has a different structure than Salagen and the choice of medication (Salagen or Evoxac) is a matter of patient preference, as side by side comparisons have not yet been presented.

Another approach to dryness is to help break up the thick, sticky secretions. Agents that contain iodides include 10% saturated solution of potassium iodide (SSKI) or organidin (both tablets and liquid). Other agents have properties similar to cough syrups (guaifenesin) such as Humabid. Bromhexine, a cough syrup available in Europe, but high doses are required and the drug is not very effective. Our experience and that reported at the National Institutes of Health indicates that medications may help some patients with relatively early or mild dry mouth (xerostomia) but are probably not as useful as either Salagen or Evoxac.

Research at the University of California in San Francisco found that many of the symptoms of painful mouth and burning tongue were due to a chronic Candida (yeast) infection and could be improved by treatment with Nystatin or chlortrimazole tablets. These tablets (also called troches or pastilles) are sucked like a "life-saver" (once or twice a day) and suppress yeast in the mouth that secrete toxins and cause a painful mouth. The clinical improvement may not be apparent for at least 3-4 weeks, so be patient. Treatment of this problem is particularly difficult in the patient with dentures, since the denture must be concurrently treated with the mucosa. Perhaps the most effective treatment for the mouth is the use of Nystatin vaginal suppositories slowly dissolved in the mouth with sips of water twice daily for about 1 month. Although the vaginal suppositories have a bitter taste, other oral forms of antifungal therapy contain a high level of sugar to improve taste and contribute to dental decay. Chlortrimazole vaginal tablets are also available and

may be used in the same manner. In some patients where the oral infection is significant, a one week course of an oral anti-yeast medication such as nizoral may be helpful to control the process.

In patients who wear dentures, recurrence of the yeast infection is very common. In order to help prevent these relapses, the dentures must be carefully cleaned with a toothbrush then soaked overnight in benzalkonium chloride (for example, a 1/200 dilution of surgical scrub solution [Zephiran]). Nystatin powder should be applied to the fitting surfaces of the dentures before reinserting.

B. The Dry EyesThe administration of artificial tears (designed to replace the diminished aqueous or "water" component of tears in Sjögren's patients) gives considerable relief to most patients, but disabling symptoms may persist in some patients. The choice of artificial tears (Table 5) in an individual patient is based on several variables. First, does the eye drop feel comfortable immediately upon instillation into the eye? In some cases, burning may be due to the preservative, and you may wish to try an artificial tear with a different preservative. Several types of artificial tears are preservative-free (Table 5). In patients who require the frequent use of artificial tears, it has been suggested that "preserved" tears should not be used more than every two hours to prevent the problems associated with "preservative buildup." In this situation, the use of a "preserved tear" can be alternated with a "preservative-free" tear. It is important to remember that all artificial tears are not the same and that the patient may have to "educate" the local pharmacist who may substitute if sometimes he does not have the requested artificial tear in stock. We ask patients to try several different preparations sequentially in order to identify those that seem most tolerable.

The second point in evaluating an artificial tear preparation is "Do the drops last long enough?" If the artificial tears are beneficial but the symptoms return relatively soon (i.e., in 1-2 hours), then an artificial tear that is thicker or more viscous might be tried. If the tear preparations still do not last long enough, closing the tear drainage ducts (punctal occlusion) should be considered. The "puncta" are small openings at the inner corners of the eyelids. Under normal conditions, the tears use these "drains" to exit the eye. Thus, narrowing these puncta (on a temporary or reversible basis by inserting small plugs, or on a permanent basis by sealing them with an electric cautery probe, on an outpatient basis) will mean that artificial tears will remain for a longer period of time in the eye. It used to be common to use a "temporary" plug made of collagen, but the results are so inconsistent that they are not frequently tried. If a punctal plug is to be used, the intracannicular plug (that does not protrude into the ocular surface) seems to be best tolerated. This is in contrast to the older style plugs that had a small "cap" on the top that could rub against the ocular surface.

Third, what is the relative expense and convenience of the artificial tear? Unpreserved artificial tears are packaged in very small quantities, so their cost is relatively high. Some companies provide artificial tears to severe dry eye patients at "wholesale" cost. It does not hurt to ask your ophthalmologist if he/she can help you get artificial tears at a lower cost.

Fourth, visual problems may wax and wane, particularly in association with the seasons when dry winds are prevalent. When patients can identify exacerbating problems, increased frequency of artificial tear application should be started before symptoms develop in the hope of preventing objective eye findings. The use of humidifiers at night, wrap-around sunglasses, and even goggles (sold at ski shops) are often helpful. Sudden worsening of ocular symptoms should always suggest possible ocular infection. In patients with associated diseases such as rheumatoid arthritis, other causes of eye pain such as "scleral" lesions or vasculitic lesions also must be considered.

Fifth, do the artificial tears that previously worked currently seem inadequate? Failure to achieve adequate results with an artificial tear may be due to several causes. As noted above, the change in environment (i.e., Santa Ana wind conditions or being in a low humidity site such as an airplane or an air conditioned department store) or medications (such as cold remedies) may cause a previously effective treatment regimen to be inadequate. Also, patients may progress from mild eye dryness or more severe dryness if the Sjögren's syndrome leads to more destruction of lacrimal glands.

In patients in whom adequate control of dry eyes has not been achieved with artificial tears and use of stimulating drugs (i.e. Salagen or Evoxac), closing the ducts at lower eyelids (called the puncta) might be considered. Tears normally are pumped off the ocular surface through the puncta and blocking these ducts will cause a longer retentio time for instilled tears. Although several types of punctal plugs are available, we have had the best luck with "intracannicular plugs" since these do not protrude into the ocular surface and can be removed without undue trauma to the duct in the future.

Finally, other causes for persistent or increased eye symptoms must be considered. Corneal abrasions (a scratch on the surface of the eye is more common in dry eye patients) or infection of the eye (often associated with a new type of pus-like discharge) may cause sudden worsening and must be promptly treated. Also, irritation of the glands in the eyelid may occur and is called "blepharitis." This cause should be suspected when swelling and redness of the eyelid occurs. This may be due to a low-grade infection or sometimes due to irritative effects of preservatives in artificial tears or ointments. One part of the treatment for blepharitis is to keep the eyelids clean using "baby shampoo" or a special product

called “eyelid scrub.” In some patients with blepharitis, infection of the meibomian glands (in the eyelids) may require treatment with a low dose of antibiotic (such as tetracycline or doxycycline) for several weeks.

A common problem when increasing irritation occurs is the question of preservative sensitivity from the artificial tears (requiring substitution of an alternative tear drop) as opposed to simple under treatment with lubricants due to worsening dryness. If using the present eye drops more frequently improves the symptoms, then more aggressive treatment is needed. If more frequent use increases the irritation, then use of non-preserved tear drops or drops with an alternative preservative should be tried. Do not delay seeking care if the symptoms do not resolve rapidly as serious infection or erosions may be present that threaten vision.

In addition to artificial tears during the day, lubricating ointments and/or gels at night also play an important role in the treatment of dry eyes. Since ointments usually cause significant blurring of vision they are generally used at bedtime. Sometimes the blurring persists in the morning and can be minimized by using only about 1/8-inch of the ointment at bedtime. It is a common mistake to use too much lubricant at bedtime. There are several different brands of ocular ointment (Table 5). As with artificial tears, they differ in their composition and preservatives. Thus, patients may tolerate some brands better than others.

In theory, soft contact lenses might help spread the tear film over the eye or prevent evaporation of tears. Some types of contact lenses absorb tear fluid as a way to maintain their rigidity and thus further diminish the amount of tears available to protect the eye. Also, great care must be taken to avoid infections and prevent damage to the cornea in dry eye patients who wear contact lenses. Rarely, a partial tarsorrhaphy (sewing the lateral portion of the eyelids together) may be required.

C. Nasal Dryness, Sinusitis, and Upper Airway Dryness

Many Sjögren's patients complain of nasal dryness and have symptoms of sinusitis with postnasal drip. In our experience, Sjögren’s patients do not get a higher frequency of sinusitis infections than other individuals. However, they tend to last longer and have a higher chance of persisting longer with “postnasal” drip and cough, or developing into a bronchitis or pneumonia. These complications occur because of decreased secretion of glands lining the nasopharynx, leading to crusting of mucous secretions that block the airways and predispose to infection. Our initial approach is to provide increased moisture to this region by use of normal saline sprays (Ocean) and humidifiers at night (Table 6). Also, “lavaging” the sinuses (i.e., rinsing them out with a mild solution of salt water) after loosening the secretions with a humidifier is often very useful in breaking the cycle of repeated sinus and

upper respiratory tract infections. “Ocean” spray is simply a brand name for a solution of salt water that helps restore humidity to the nose. It is simple to make your own salt water spray by adding one teaspoon salt to one quart of deionized water and boiling to fully dissolve the salt. The Ocean spray container can then be refilled with homemade salt water. There are many different types of cool mist humidifiers that vary in size and cost. We recommend the small portable units (choose one that is silent and easy to clean/refill), and not the large humidifier units that are built into the house's furnace/air conditioning systems. The large room units may become contaminated with yeast or fungus that can subsequently lead to “allergic”-type reactions. This problem has not been encountered with the small portable units where the water is changed daily. In areas where the water is “hard” (i.e., contains large amounts of calcium and other salts), “distilled” water (similar to that used for irons) may be less irritating than water from the tap.

In patients with persistent or recurrent sinus blockage, it is important to keep the nose open since breathing through the mouth is a frequent cause of increased dry mouth and the problems described above. In addition to the Ocean spray, it may be beneficial to learn to “lavage” the sinuses to remove the dry, crusted secretions. This is easily performed by the patient using an irrigation syringe (similar to the syringe used for basting a turkey) or a Waterpik (set for the lowest pressure delivery level). In patients with persistent sinus symptoms, it is also useful to obtain a “nasal smear” to determine if allergic factors (indicated by presence of eosinophils on the smear) are playing a factor. Topical nasal sprays (such as Beconase, Nasal AQ, or Flonase) may be helpful in these patients, especially after lavaging (Table 6). In the setting of sinusitis, it is always important to notice if the color of secretions changes from clear to dark green; the latter situation may indicate the occurrence of bacterial infection and necessitate treatment with antibiotics. The diagnosis of sinusitis is confirmed by sinus x-ray with air-fluid levels and purulent sinus drainage. When symptoms of sinus infection are persistent despite the above treatment measures, the possibility of an “abscess” within the sinus must be considered and this may require surgical drainage. In order to determine if the sinus infection requires this treatment, A CAT scan of the sinuses is performed. The radiologist can perform a “limited” CAT scan at a much lower cost than a full CAT scan. If an abscess is detected, it may be necessary for an ENT specialist to establish sinus drainage, obtain definitive cultures and treat with a specific antibiotic.

D. Skin Dryness

Dry skin and lips are common complaints in Sjögren’s syndrome. Topical treatments with creams and lotions (Table 7) are often helpful. Creams are distinguished from lotions by being “greasier” than lotions, which often contain oil/water mixtures. Creams and ointments are preferred since they better “seal” in necessary

moisture. In general, we suggest applying the creams after a shower or bath while the skin is still moist. Alternatively, the cream can be applied to dry skin directly after moistening with a damp cloth. In many patients, moisturizing agents such at cetophile, carmol or lachydrin prove useful in helping to seal the moisture into the skin. Cosmetics such as lipstick can be applied 5-10 minutes later. Cracking at the angles of the cheek (cheilitis) is often due to Candida infection and will not effectively heal until a topical cream (such as Spectazole or Loprox) is applied (Table 7).

E. Gynecologic Issues

Vaginal dryness often leads to painful intercourse (dyspareunia). It is important to be reassured that this does not occur in all Sjögren's patients, even those with severe mouth and eye dryness. A gynecologic exam is useful to rule out other causes of painful intercourse and other causes of vaginal dryness. When it does occur as part of Sjögren's syndrome, the spouse needs to be reassured that this is a "physiological" problem and not related to a failure of sexual arousal. Sterile lubricants such as Astroglide, KY jelly or Surgilube are helpful. The Sjögren's patient currently has many more options regarding safe and effective vaginal lubrication than every before. Lubricants such as Maxilube and Astroglide have slightly different characteristics when compared with KY jelly or Surgilube and yet share the common characteristics of being water-soluble and nonirritating. This also holds true for the new non-hormonal vaginal moisturizer Replens, which may be used, unassociated with intercourse. For those patients who do not like the gel-type lubricants, there is now available Lubrin vaginal inserts. Finding the right preparation for a specific individual is often a matter of trial and error inasmuch as satisfaction with each lubricant is a matter of personal preference. The patient needs to be frank with her physician regarding her satisfaction or dissatisfaction with a particular preparation. The external use of preparations containing petrolatum or oils which "seal in" moisture, such as Vaseline or cocoa butter, may lead to maceration of the vaginal lining and are to be avoided.

Vaginal dryness in perimenopausal or postmenopausal women is often related to vaginal atrophy because of declining estrogen levels and therefore responds to vaginal estrogen creams. Cortisone creams are not beneficial in this situation. If vaginal yeast infection occurs, prompt treatment with clotrimazole cream or suppositories (Gynelotrimin) is effective and safe. On the external vulvar surface, dryness may be treated with lubricating creams as you would other skin surfaces (see section on skin dryness). Several patients have reported considerable satisfaction with the use of a thin film of vitamin E oil used on the vulva once or twice a day.

An issue of concern to female Sjögren's patients has been whether or not estrogen replacement therapy at the time of menopause is harmful to their condition. With regards to estrogen replacement in general, the clinical evidence is controversial whether the risks of blocking osteoporosis and reducing cardiovascular mortality adequately offset the small increase in risk in breast cancer. However, some women feel that estrogen replacement improves their quality of life in terms of mood elevation, by eliminating hot flashes and hormone-related vaginal dryness. Earlier investigators were concerned that estrogen might have a negative influence on Sjögren's based on animal studies. At our clinic, we have not seen any deterioration of Sjögren's syndrome related to either estrogen replacement therapy or low estrogen forms of oral contraceptives. Because of this, we encourage adequate estrogen replacement for the properly screened postmenopausal Sjögren's patient who feels that it improves their quality of life. However, other therapeutic alternatives for osteoporosis (Fosomax and Actonel) and for lowering cholesterol are now available and estrogens are now not the agents of choice for these medical issues. .

Many women with Sjögren's syndrome are interested in the risks of pregnancy and risks to the baby. Obstetrical authorities report slightly higher rates of recurrent fetal death and congenital heart block in those pregnancies complicated by maternal autoimmune disease. In rare patients, fetal loss has been associated with presence of the antibodies called "antiphospholipid antibodies," "lupus anticoagulant" and anticardiolipin antibodies. Congenital heart block is an abnormality of the rate or rhythm of the fetal or infant heart. Certain auto-antibodies, such as an antibody called "anti-SS-A," have been associated with congenital heart block in the newborn. These autoantibodies may be present in patients with systemic lupus erythematosus and with Sjögren's syndrome, as well as in patients with no apparent disease. However, it is important to reassure patients planning families that the vast majority of patients with Sjögren's syndrome have babies with no congenital abnormalities. Thus, we encourage family planning to be conducted without this being a major consideration. Nevertheless, it is important for patients anticipating pregnancy (or those with multiple prior miscarriages) to have screening blood tests and that their pregnancies require supervision by obstetricians experienced in handling patients with autoimmune diseases. If a pregnant patient requires corticosteroids for their medical condition, we suggest decadron (rather than prednisone) since it crosses the placenta and will provide protection to the fetus. A team approach combining both rheumatology and obstetrics can be used to optimize the outcome for both mother and baby. In our experience, flares of Sjögren's have been common after delivery and we often recommend steroid coverage at the time of delivery and in the post partum period in some patients.

F. Myalgias and Arthralgias

Physicians frequently use terms like arthralgia and arthritis. The former term means that the joint aches and the latter term means "inflammation" as indicated by the presence of heat, redness and swelling. In a similar sense, myalgia refers to aching of the muscle and myositis to actual muscle inflammation. Finally, neuralgia refers to "nerve pain" while neuritis or neuropathy refers to inflammation of the nerve.

The distinction between arthralgias and arthritis can often be made on clinical examination. However, more sensitive tests including x-rays or bone scans may be required. In the case of muscles, blood tests and, occasionally, electrical stimulation tests [called electromyography (EMG) and nerve conduction velocity] are useful.. The treatment of arthralgias usually begins with an anti-inflammatory agents such as voltaren (diclofenac), clinoril (sulinac), naproxen (alleve), or ibuprofen (advil). These agents may increase fluid retention, blood pressure or cause gastrointestinal upset or bleeding. In patients with a history of ulcer (or taking corticosteroids), a more expensive anti-inflammatory are the newer agents called "cox-2" inhibitors such as vioxx (rofecoxib) or celebrex (celecoxib). These agents have less bleeding tendency but recent studies have shown that older patients need to take a baby aspirin along with the cox-2 drug in order to reduce frequency of either heart attack or stroke. When the cox-2 and baby aspirin are taken together (i.e. the normal current recommendation), it remains unclear if the initial benefit in GI bleeding will be worth the significant increase in cost. Thus, newer (i.e. cox-2 drug) does not necessarily equate to more efficacious or significantly increase in safety in all patients. Whether a traditional non-steroidal or a cox-2 drug is used, the patient still needs to be monitored for elevation of blood pressure, fluid retention, and effects on the liver as well as skin rashes.

Prednisone (a corticosteroid) is extremely effective but has long term side effects including hypertension, weight gain, irritability, sleep disruption, osteoporosis, glaucoma and diabetes. These side effects are largely dose related and start to increase in frequency when the dose is above 7.5 mg per day. The old joke in rheumatology is that doctors only have one efficient drug (i.e. prednisone) and the art of rheumatology is how to get the patient off. But in summary, the steroids work and often are required in short term courses until another medication can be used to control the symptoms and allow the dose to be tapered or eliminated.

In patients with more severe arthralgias or arthritis, stronger medications called "disease modifying anti-rheumatic agents" (DMARDs) need to be used. Perhaps the oldest and safest is hydroxychloroquine (Plaquenil), which is used in a dose based on weight (up to 7 mg/day per 2.2 pounds of body weight). This drug has a slow onset and takes about 3 months to kick in. The drug labeling warns of build up in the retina. This warning derives from many years ago when the drug was used in

high dose (often up to 15 mg per 2.2 pounds of body weight). When the correct dose is used, the risk of retinal damage is estimated to be about 1 in 10,000 (which was not significantly different than control groups). Nevertheless, for medical-legal purposes as well as for patient protection, we advocate that the patient get an eye check about 6 weeks after starting and then every 1-2 years. In this way, patients who do not tolerate the medication (usually GI upset or a rash) will not have the added expense of pre-therapy eye check and since the potential for eye buildup would require years, the patient is at no risk by waiting this short interval and may save money on one less doctor's visit.

In patients with more significant arthritis or difficulty in tapering corticosteroids, the next DMARD frequently used is methotrexate. In high dose such as 500 mg, this drug is a chemotherapy (i.e. for leukemia) and causes lots of problems such as hair loss and low white cell count. However, in Sjögren's syndrome it is used as a once a week dose of 7.5 to 15 mg. At this dose, there is very little side effect and is widely used without problems in patients with rheumatoid arthritis and systemic lupus. Nevertheless, patients with liver disease (either alcoholic or hepatitis C infection) probably should avoid this medication and routine (every 3 month) blood checks of white blood count and liver tests will further improve safety. As in the treatment of rheumatoid arthritis, other drugs including Arava (leflunomide) have proven useful either alone or in combination with methotrexate. Other agents such as azulfidene and cyclosporin have proven less effective and had more side effects. New potent drugs called Enbrel or Remicade (called biologic agents that inhibit tumor necrosis factor) remain very effective at decreasing joint pain but may exacerbate other features of the autoimmune process (such as low platelet counts) and have even been associated with reactivating infections such as tuberculosis or multiple sclerosis. For this reason, we try to avoid biologics in our patients.

In some patients, inflammation of the nerves may produce symptoms of pain, weakness or numbness. The nerves may be affected at many different sites; involvement of the brain is termed central nervous system, of the spinal cord is termed a myelopathy, and of the nerves that leave the spinal cord is termed peripheral neuropathy. If inflammation of the brain is suspected, procedures such as MRI (magnetic resonance imaging) may be required. The brain MRI is done after an intravenous infusion of a material called gadolinium. If the small blood vessels of the brain are involved, they become "leaky" and this is termed "enhancement" on the MRI. Other problems detected on the MRI are multiple sclerosis like lesions, blood clots and strokes. In our experience, brain inflammation is uncommon but has been reported in higher frequency at another medical center.

There may be inflammation of peripheral nerves (those that have exited from the spinal cord). The involvement of the nerves can cause weakness or numbness. The EMG and nerve conduction study may be required for diagnosis in this situation.

Also, it is important to remember that many other common problems result in nerve, muscle or joint pain. For example, a pinched nerve at the level of the spine may cause numbness and weakness in an arm or leg. A torn cartilage in the knee or a degenerated disc in the back may lend to joint pain or muscle spasms. These common problems are not due to Sjögren's syndrome. Too often, patients and their physicians may not look for "the obvious" causes of symptoms and simply blame the problem on Sjögren's syndrome. This delays the institution of the correct therapy for the problem.

G. Fatigue

Fatigue is probably the most common complaint in patients with Sjögren's syndrome. As mentioned above, three types of fatigue should be considered and this section will emphasize the therapeutic approaches. To help determine whether fatigue is due to active inflammation, blood tests called "sedimentation rate" or "C-reactive protein" are ordered by your physician, since these tests are usually elevated by the same interleukins that cause fatigue. The general approach to fatigue associated with an active immune response is similar to the treatment of SLE not involving critical internal organs. The initial medication is usually an anti-inflammatory medication such as naproxen and in some cases an agents such as hydroxychloroquine (an anti-malarial class of medications). This medication is given on the basis of weight (no more than 7 mg per kilogram of body weight per day). The tablets come in 200 mg size and the general dose is 200 to 400 mg per day. The package insert describes blindness and build up in the retina. This is very, very rare at the correct dose and is estimated at less than 1 person in 10,000 who receive this drug. In Europe, they no longer even do ocular screening since the side effect is much less frequent than the risks of not treating the active disease process. We generally get the first eye check up at 3 months after starting and then about every 2 years. However, any change in vision demands immediate eye check up to look for hydroxychloroquine or other causes such as glaucoma (particularly if the patient is on steroids). Hydroxychloroquine is slow to take effect (about 6 wks) and sometimes other medications including prednisone are used in a tapering dose until the hydroxychloroquine has time to take effect.

If the immune tests remain elevated and symptoms persist despite the hydroxychloroquine, the next medication used is often methotrexate given as a weekly dose. This medication has potential liver toxicity and should not be taken by heavy drinkers or patients with hepatitis viral infection. However, liver tests are monitored and dose adjustments are made similar to guidelines used in RA patients taking this medication.

Many other medications, including the newly approved biologic agents (such as Enbrel and Remicade), have recently been highly advertised for rheumatoid

arthritis. However, these medications are very expensive, not approved for SS (and thus not covered by insurance) and have unknown long term side effects including the potential for lymphoma, increased infections such as tuberculosis and demyelinating disorders such as multiple sclerosis. Until carefully controlled studies comparing TNF inhibitors and comparable agents such as methotrexate are available, it is not clear that they will be more effective than available therapy. Also, it is probably prudent to defer these strong agents until longer term safety data is available on complications such lymphoma and demyelinating diseases, since there may already be slightly higher frequency of these problems in Sjögren's patients that could be exacerbated by these TNF inhibitors.

A second type of fatigue is "morning fatigue," where the patient arises in the morning and does not feel that he/she has obtained an adequate night's sleep. This is also quite common in Sjögren's syndrome and may exist in addition to "inflammatory" fatigue. For example, patients may have inadequate sleep due to joint or muscle pain. Also, Sjögren's patients often drink a great deal of liquid during the day because of dry mouth and throat. Then at night, the patient may be awakened three or four times to urinate. This disrupts the sleep pattern and leads to morning fatigue. When this is the case, it is best to treat the symptoms directly and better sleep should follow. For example, humidifiers and oral lubricants (i.e., saliva substitutes) at night might be beneficial. Nonetheless, there may be periods when one doesn't sleep well, and it is important not to allow certain negative sleep habits to become ingrained. All persons, especially those with a tendency to poor sleep or daytime fatigue should adhere to the following general suggestions for good sleep:

A third type of fatigue is "metabolic" and may result from hypothyroidism. Replacement with synthroid is easier to measure and adjust than some of the more recent suggestions to use thyroid (armour extracts) in our experience. Other suggestions have been low DHEA, which is a precursor of testosterone that normally is made in low levels in females. The levels of DHEA may be diminished in both menopause or in corticosteroid treated patients. If the DHEA level is diminished, this compound can be supplemented with DHEA preparations (usually 25-50 mg/day) which are available without prescription. In some postmenopausal patients, estrogen replacement may increase the sense of "well being." We have not found flares of Sjögren's in patients, in contrast to the flare of autoimmunity in some animal models of disease after estrogen replacement. If estrogen replacement is used (after approval by gynecologist and making sure no breast carcinoma or blood clots), then we have preferred natural estrogen by continuous delivery such as vivelle dot (a transdermal system) and a natural progesterone (prometrium). Finally, some patients note a type of fatigue which is "orthostatic" (i.e. a sense of lightheaded on position change from supine to sitting, as sometimes occurs during the flu); this condition is documented by noting the extend of blood pressure change

and can be treated with low doses of florineff or a shorter acting medication called proamitine in some patients.

In terms of sleep disruption (non-restorative sleep), this problem is so common among Sjögren's patients that several general guidelines might be mentioned.

1. Maintain a regular and consistent wake-up time. Do not oversleep or spend excessive amounts of time in bed.
2. If unable to sleep, it is better to get up and do something else that is quiet, restful, and enjoyable, such as reading, knitting, or doing a puzzle. Do not lay in bed and try too hard to sleep.
3. A steady daily amount of exercise probably deepens sleep. Many patients report that a simple exercise such as sit-ups prior to bed and then a warm shower help relax the muscles and give a more restful sleep.
4. Stress reduction techniques such as meditation, biofeedback, or progressive relaxation are encouraged. In patients with muscle spasm (particularly back pains), an organized program such as Tai-chi proves helpful in addition to traditional methods of physical therapy.
5. Caffeine should be avoided after lunch, and alcohol should be avoided after dinner. In some people, even one cup of coffee or one alcoholic beverage is enough to disturb sleep.
6. The bedroom should be quiet, dark, and comfortable. During the daytime, exposure to sunlight for even one hour at a regular time can strengthen circadian rhythms and improve the quality of sleep. Especially in San Diego, get outside for your lunch hour or take a walk after dinner.

Sometimes following good sleep habits is not enough to improve the sense of daytime fatigue and poor sleep. If this is the case, a specific evaluation for sleep disorders can be done. Certain people may have a higher risk of physiologic sleep disorders. In our experience, patients with Sjögren's frequently have sleep disturbance due to nocturnal myoclonus (a spontaneous muscle cramping) that occurs at night and disrupts the amount of time spent in "restful" sleep. Some patients respond to quinine and vitamin E at bedtime. Some patients respond to medications for Parkinson's disease (Sinemet and Mirapex), although these may increase dryness. Other patients require a medication such as Klonopin (clonazepam), a member of a drug family called benzodiazepams (that includes Valium and Ativan). These drugs have the ability to prevent muscle spasms and were first developed to prevent muscle rigidity associated with seizures. Thus, patients who look up Klonopin are surprised to see that it was first approved for children with seizures. This is because Klonopin reduces severe muscle spasms, a life-threatening part of seizures in children. However, Klonopin is used in much lower doses to reduce the muscle spasms associated with nocturnal myoclonus. Like its parent compound Valium, Klonopin also has "anti-anxiety" activity and has other uses in addition to nocturnal myoclonus. A word of caution, higher doses of

klonopen or Valium can be highly habit forming and need to be scrupolosly avoided in any individual with a tendency to substance dependency. To avoid higher doses of klonepin, another drug (Trazadone) is often used in conjunction at bedtime. Other medications such as Elavil (amitriptyline) or Pamelor (nortriptyline) are commonly prescribed for sleep disorders but are generally not well tolerated by Sjögren's patients due to their side effect of increased dryness.

Sleep disruption can occur due to sleep apnea. Sleep apnea is suspected in patients who snore loudly or awake at night gasping for breath. Patients with recent weight gain (often due to corticosteroids) may develop sleep apnea. This problem requires the expertise of a sleep center for evaluation and treatment.

Finally, some patients may experience fatigue or lightheadedness in the morning when they arise from a supine position. In these patients, the possibility of positional (orthostatic) hypotension needs to be considered. This is part of an imbalance in the nervous system called an autonomic neuropathy. It is found in SS patients as well as in patients with diabetes and other neurologic diseases or as a side effect of many medications used for blood pressure (including diuretics) or neuropathy. The patient should obtain a blood pressure cuff to measure the pressure when supine and when standing. The diagnosis is confirmed by the cardiologist performing a "tilt table test." The problem is that the blood pressure drops too low and leaves the blood supply to the brain inadequate. There are a variety of older medications (such as florineff) and newer shorter acting medications (such as proamitine) that may prove helpful.

H. Depression in Sjögren's Syndrome

Depression can present in many forms, including difficulty concentrating, poor appetite, or a sleep disorder. The precise role of inflammation and hormone imbalances associated with Sjögren's syndrome as a contributing factor to depression remains unclear, but certainly depression is caused in part by neuro-chemical alterations in the brain. In particular, abnormalities in serotonin and norepinephrine metabolism may contribute and this is the basis for current therapies including drugs such as Prozac and Effexor.

Stress, poor sleep, and chronic illness can all contribute to depression. When antidepressant medications are used to help regulate sleep patterns and treat fatigue, drugs lacking anticholinergic side effects are preferred. As mentioned earlier, certain antidepressants such as tricyclics (Elavil and Pamelor) and monoamine oxidase (MAO) inhibitors may greatly increase dryness and should be avoided. A second class of antidepressants with less dryness include trazodone (Desyrel); newer members of this family include Serzone.

The most widely used class of antidepressant drugs is called serotonin re-uptake inhibitors (SSRI). These include Celexa, Prozac, Paxil, Zoloft, Luvox and Effexor. In general, we usually start with Celexa since it is less sleep disruptive than Prozac and has less weight gain than Paxil. Recent studies in patients with fibromyalgia indicate that higher doses of Prozac (40-60 mg/day) or Celexa (40-60 mg/day) may be required than are generally given by primary care physicians for this problem and that lack of efficacy may be due to under dosing or escalating too rapidly to full dose. The incidence of increased dryness (and other side effects including sleep disruption) appears variable among different patients and a careful diary by the patient may help the physician in the selection of the correct drug. As noted above, the therapy of depression will likely provide a new generation of drugs that will prove helpful to treat the fatigue in patients with autoimmune disease.

XI PATIENT SUPPORT GROUPS

The increasing recognition of Sjögren's syndrome has led to the formation of patient support groups. One group, called the Sjögren's Syndrome Foundation, puts out a monthly newsletter, *The Moisture Seekers*, and has local chapters in many cities including San Diego (local contact persons are listed in some issues of *The Moisture Seekers*). Although we recommend these newsletters as a source of patient information, we wish to caution you that some of the material may be controversial and may conflict with our opinions. Nevertheless, we strongly believe that patients should have access to all points of view (including those opposed to ours) and we are happy to discuss our reasons for/against any specific suggestions. Just do not take everything that is in a newsletter (or that we say) as "gospel." Similarly, the periodic meetings of patient support groups are a potential source of helpful information and emotional support. However, they also may be a source of misinformation. So approach patient support groups with an open mind as if you were competitively shopping for an important item. Whether you belong to a support group or not, it is important to surround yourself with people who believe in ""wellness" behavior rather than with individuals who are chronic complainers.

XII. ROLE OF THE DIET AND NUTRITION

Patients frequently ask about the role of diet either in causing their disease or in their treatment. No definite answers are known, but environmental agents (perhaps even food antigens) may play a role. In general, most patients have found that it is helpful to avoid chocolate, nuts, undissolved salt, vinegar and vinegar prepared foods, strong cheese (Swiss, cheddar, bleu, Roquefort), high acid foods (tomatoes, citrus fruit and juices) and alcoholic beverages. Many patients find yogurt (no berry flavors, diluted baking soda, or cultured buttermilk as a mouthwash helpful. Be aware of lactose intolerance if diarrhea develops. In many

autoimmune disorders, some patients find that red meat, heavily processed foods, and foods containing sugar makes their overall systemic symptoms worse (in addition to the detrimental effects of sugar on the oral status). Also avoid tobacco and commercial mouth rinses that contain alcohol. If you are going to chew gum, it should be sugar free (not sugar low).

There is great controversy about the role of diet and autoimmunity, with some physicians emphasizing that there is no objective evidence. Although there may not be a single agent that adversely affects all patients, a careful look at your diet is worthwhile. There are examples where dietary factors trigger the immune system. One of the best examples of diet-related autoimmune disease is celiac sprue, where autoimmune reaction against gliadin (a wheat-derived product) plays an important role. At a molecular level, the gliadin resembles a viral-encoded protein and thus the body mounts an "antiviral" response every time it encounters this food antigen. It is possible that other foods may provoke and adversely activate the immune system by mechanisms that we do not understand. It would be helpful if we had reliable methods to detect specific "food allergies" in patients. Despite two decades of trying to develop such tests, there are still no reliable methods. However, some unscrupulous individuals advertise special blood tests for "food allergy." These tests have <u>not</u> been shown to have merit and circulating antibodies against specific food antigens have not been demonstrated in Sjögren's syndrome. We do recommend that patients avoid candy and products containing sugar, which may cause dental cavities and increased gingival disease.

Recent interest has centered around the possible role of fatty acids that are precursors of prostaglandins and/or leukotrienes, which play an important role in the inflammatory response. One preliminary report suggests a deficiency of prostaglandin E_1 (a derivative of fatty acids) in Sjögren's patients that were treated with dietary supplements of fatty acids. Recent studies in rheumatoid arthritis have shown that mild subjective improvement and minor degrees of improvement in joint swelling could be achieved by taking fish oil tablets containing particular fatty acids known as omega-3 polyunsaturated fatty acids. It is too early to give these fatty acids any recommendation in Sjögren's syndrome since this "medication" actually increased arthritis when fed to rats.

Little information is available on the beneficial role of vitamin or mineral supplements in Sjögren's syndrome. Certainly, a daily multi-vitamin seems justified, particularly since dietary food intake is often altered due to tooth loss/gingival disease. Although severe vitamin A deficiency can cause dry eyes, the clinical features of this dry eye syndrome are different from those in Sjögren's syndrome. Further, serum vitamin A levels are normal in Sjögren's patients and excessive intake of this vitamin can cause fatal liver damage. Based on reports that zinc was helpful in reducing stomatitis in patients after head and neck irradiation,

we tried zinc sulfate (220 mg/day) without significant improvement in most cases but a few patients had improved sense of taste. However, double-blind studies on large numbers of patients will be required before the role of vitamins and dietary factors can be adequately assessed. We have suggested daily yogurt (especially low fat) since this has had a beneficial response in decreasing oral Candida infections, increasing saliva flow and thus decreasing mouth discomfort.

XII. HEARTBURN AND ESOPHAGEAL MOTILITY IN SJÖGREN'S SYNDROME

Saliva normally plays a major role in neutralizing gastric acidity. Thus, symptoms of "heartburn" or "hiatal hernia" are common in Sjögren's syndrome. Gastric hyperacidity can be partly overcome by the use of antacids (such as Mylanta II or Maalox II) after meals and at bedtime. Also, elevation of the head of the bed on 2-inch wood blocks provides a way to reduce the gastric acid from washing back into the esophagus at night. In some patients with severe problems of "heartburn," the medicine sucralfate (Carafate slurry) has been helpful. This medicine was designed to "coat" the esophagus and stomach of patients with ulcer disease. However, sucralfate coating of the stomach might interfere with the absorption of certain other medications so be certain to check this possible drug interaction with your physician and pharmacist.
For more severe heartburn, two types of medications decrease the response of the gastric mucosa to the acid or to reduce the gastric production of acid. The first type is called "H2 blockers" and includes Tagamet, Pepsid, and Zantac; each of these have recently become available over the counter. A second type of medication that reduces acid production still requires a prescription. Members of this family include Prilosec (Omerasol in Mexico), which will soon go over the counter, as well as Nexium, Aciphex, Prevacid, and Protonix. There has been debate about whether a combination of these medications is more useful than either class alone. If a combination is taken, then the acid suppressor (i.e.Prilosec like) might be taken in the morning, while the H2 blocker (i.e. tagamet) might be taken before bed. Finally, some patients who have decreased motility of the esophagus benefited from a medicine called cisapride (Propulsid). However, this medication was removed from the market in the US due to a relatively rare side effect after many years of use with a good overall safety record. Reglan, Other medications with similar beneficial effects are in the late stages of clinical development and should reach the market in near future.

Since saliva normally helps during swallowing pills, it is important to recognize that pills can become stuck to "dry" walls of the esophagus and cause painful erosions. For example, iron supplement pills are large in size and uncoated tablets may get stuck in the esophagus, leading to pain and a choking sensation. Also, certain time-release preparations tend to adhere to the esophagus in the absence of sufficient saliva. To minimize these problems, coated tablets are preferred (when

available) and medication should be taken with lots of water while sitting in the upright position (rather than lying down just after taking the pills).

XIII Hints to help your doctor get approval for the required tests and medications.

In these days of computer codes being required for insurance reimbursement (Table 9), we have listed several codes that are required for ordering a diagnostic test. If your insurance does not accept the initial diagnosis code, ask if the procedure is covered by Table 9.

When your physician orders certain medications, it is almost a guarantee that prior approval will be required. For example, you might have received a sample of medications for gastric acidity called proton pump inhibitor (such as rilosec, prevacid, aciphex). The pharmacy benefits company will want to know that you have previously failed drugs that are cheaper such as tagamet (cimetidine) or zantac (ranitidine). If you have failed these drugs and want the prilosec medication, you need to provide the doctor with the dates when you took the tagamet or zantac to help get authorization. Other medications requiring pre-authorization are the new cox-2 (vioxx and celebrex) medications. The pharmacy benefits company will want to know that you have tried at least 2 or 3 different available medications such naproxen, diclofenac (voltaren), or clinoril (sulinac) before they will approve the more expensive medication. In general, the newer medications are denied unless there is a history of ulcer or the patient is concurrently receiving steroids. Thus, we have the paradox that the physician has samples of the newest drugs to give the patient and the patient is then frustrated when the prescription for these medications are requested due to their efficacy.

XIV. PARTICULAR NEEDS OF THE SJÖGREN'S PATIENT AT THE TIME OF SURGERY

We recommend that patients bring their own medicines (including artificial tears, lubricants, and saliva substitutes) to the hospital. The patient may use their own medicines (if approved by their physician) and if they are brought to the hospital in their labeled containers and this saves not only money but also time in dispensing the same medications from the pharmacy. This is particularly true of "special" drugs for dryness of eyes and mouth that are not on the formulary of many hospitals.

Some special needs of the patient with Sjögren's syndrome are listed in Table 11.

Certain medications (especially aspirin or NSAIDs) may alter the normal blood clotting mechanisms and need to be stopped prior to surgery. In general, aspirin needs to be stopped approximately 6 days prior to major surgery, while nonsteroidal anti-inflammatory drugs (including Motrin and other over-the-counter analgesics

such as Advil) approximately 72 hours prior to surgery. The newer Cox-2 (i.e. Vioxx, celebrex) do not interfere with bleeding but it is still probably a good idea to stop them about 24 hours before surgery.

Even if you are not undergoing surgery, it is always a good idea to carry a written list of your current medicines, their doses, and any drug allergies you might have. Nothing is more annoying for the physician (and dangerous to the patient) than trying to identify the name of "some small white pill" that the patient can't quite remember in the stress of medical evaluation.

In summary, Sjögren's syndrome is an autoimmune disease of unknown cause that results in decreased salivary and lacrimal gland function. Also, extraglandular symptoms are frequently present and may occasionally overshadow the complaints of dry eyes and mouth. Although there is no cure, significant symptomatic improvement can be achieved and many serious complications can be avoided by recognition and early treatment. Research is currently focusing on the cause of Sjögren's syndrome and new methods are being developed to control the "autoimmune" phenomena responsible for Sjögren's. In an era of increasing health maintenance organizations (HMO's) and the need for diagnosis codes, it is often necessary for the patient to help their physician or dentist by informing them of currently accepted diagnosis codes. A partial listing of several useful codes is provided in Table10.

TABLE 1:

CRITERIA FOR DIAGNOSIS OF PRIMARY AND SECONDARY SJÖGREN'S SYNDROME*

(Based on the newly submitted Joint European-American Consensus Group)

I. Primary Sjögren's syndrome
   - A. Symptoms and objective signs of ocular dryness
     1. Schirmer I test <8 mm wetting per 5 minutes
     2. Positive rose bengal or fluorescein staining of cornea and conjunctiva to demonstrate keratoconjunctivitis sicca
   - B. Symptoms and objective signs of dry mouth
     1. Decreased parotid flow rate using Lashley cups or other methods
     2. Abnormal biopsy of minor salivary gland (focus score of =1 based on average of 4 evaluable glands)
     3. Abnormal salivary gland scintigraphy scan or sialogram characteristic of SS
   - C. Evidence of a systemic autoimmune disorder
     1. Elevated rheumatoid factor =1:320
     2. Elevated antinuclear antibody =1:320
     3. Presence of anti-SS-A (Ro) or anti-SS-B (La) antibodies

II. Secondary Sjögren's syndrome

Characteristic signs and symptoms of SS (described above) plus clinical features sufficient to allow a diagnosis of rheumatoid arthritis, systemic lupus erythematosus, polymyositis, or scleroderma

III. Exclusions

Sarcoidosis, preexistent lymphoma, acquired immunodeficiency disease, hepatitis C and other known causes of keratitis sicca or salivary gland enlargement. Measurements of tear and saliva flow must be made with patient off medications that can cause dryness for at least 72 hours.

**Patients must have evidence of dry eyes, dry mouth AND either a characteristic minor salivary gland biopsy (focus score greater than 1) or characteristic autoantibodies against SS-A (Ro) or SS-B(La)

TABLE 2:
CAUSES OF KERATITIS AND SALIVARY GLAND ENLARGEMENT OTHER THAN SJÖGREN'S SYNDROME

Keratitis	Salivary Gland Enlargeme
Mucous membrane pemphigoid	Sarcoidosis, amyloidosis
Infections: virus (adenovirus, herpes, vaccinia), bacteria, (especially, Staph albus., Chlamydia, trachoma)	Bacterial (including gonoc infections(e.g., infectious r Tuberculosis, actinomycos
Trauma (e.g., from contact lens), environmental irritants, and surgery (including Lasik)	Human immunodeficiency
Neuropathy including neurotropic keratitis [e.g., damage to fifth cranial nerve and familial dys-uatonomia (Riley-Day syndrome)]	Tumors (usually unilatera tumor),epithelial (adenom lymphoma, and mixed sali
5. hypersensitivity including chemical burn, and over exposure to ultraviolet lights	Excessive alcohol consump
Allergic reactions including Erythema multiforme (Stevens- Johnson syndrome)	Hyperlipemic states, espec

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TABLE 3: EXTRAGLANDULAR MANIFESTATIONS IN PATIENTS WITH SJÖGREN'S SYNDROME

Respiratory	Chronic bronchitis secondary to dryness of upper and lower airway with mucus plugging
	Lymphocytic interstitial pneumonitis
	Pseudolymphoma with nodular infiltrates
	Lymphoma
	Pleural effusions (pleurisy)
	Pulmonary hypertension, especially with associated scleroderma
Gastrointestinal	Gastroesophageal reflux (GERD)
	Dysphagia (difficulty swallowing) associated with xerostomia or decreased esophageal motility
	Atrophic gastritis
	Liver disease including biliary cirrhosis and sclerosing cholangitis
Skin and mucous membranes	dryness and increased bruising
	photosensitivity
	rashes (macular-flar and papular-raised)
	blepharitis (eyes) and oral candida (including angular cheilitis)
	Hyperglobulinemic purpura
	Raynaud's phenomenon and digital ulcers
	Vasculitis--similar to SLE patients
Endocrine, neurologic, and muscular	Thyroiditis
	Peripheral neuropathy involvement of hands and/or feet
	Mononeuritis multiplex
	Myositis
Hematologic	Neutropenia, anemia, thrombocytopenia
	Pseudolymphoma
	Lymphadenopathy
	Lymphoma and myeloma
Renal	Tubular-interstitial nephritis (TIN)
	Glomerulonephritis, in absence of antibodies to DNA
	Mixed cryoglobulinemia

Amyloidosis
Obstructive nephropathy due to enlarged periaortic lymph nodes
Lymphoma
Renal artery vasculitis

TABLE 4: COMMERCIAL PREPARATIONS OF ARTIFICIAL SALIVA*

	Manufacturer	contact
A. Mouth and Nasal Preparations		
Biotene and Oral Balance (www.laclede.com)	Laclede	800-922-5856
CosSysII (www.rowpar.com)	Rowpar	800-643-3337
Dental Care Toothpaste	Arm & Hammer	www.myoralcare.com
MouthKote, Pretz, Oragesic (www.parnelllpharm.com)	Parnell	877-457-4276
Saliment	Ferring	
Xero-Lube	Scherer	
Saliva Substitute	Roxane	
Salivart	Westport	

TABLE 5: COMMERCIAL PREPARATIONS OF ARTIFICIAL TEARS

Artificial Tears and Lubricants

Refresh, Refresh Plus	Allergan	www.allergen.com
Bion Tears	CIBA	
Hypotears and Hypotears PF Hypotears Ointment	IOLAB	
Tears Naturale Duratears ointment	Alcon	
Murocel Tears Clerz Tearisol Comfort Drops	Bausch & Lomb	
Thera Tears	Advanced Vision Research	
Ocular Lubricants		
Refresh PM	Allergan	
Gen Teal gel	Novartis	

Punctal Occlusion
Temporary collagen plugs (unreliable)
Intracannicular plugs
Herrick plugs (may cause irritation if protrude into ocular surface)
*

.

E. Blepharitis

Baby shampoo	Johnson & Johnson
I-Scrub	Cooper
EV Lid Cleaner	Eagle Vision
Ocusoft Scrub	Ocusoft

F. Punctal Plugs
temporary (collagen)
intracannicular plugs
Herrick plugs

*All products in each category are other not equivalent to each

TABLE 6: SINUSITIS

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1. Humidifier (i.e., Cool Mist Vaporizer)

2. Ocean spray (salt water) to irrigate sinuses. Can make solution by dissolving 1 teaspoon salt in 1 quart distilled water.

3. Lavage of nasal passages with saline
   - Basting syringe
   - Waterpik--smooth the end of applicator and set at lowest setting
     Instrument designed for lavage

   Specific machines made for sinus lavage

4. Decongestants (with less drying side effect)
   - Clariten and clarinex
   - Allegra
   - Zyrtec

5. Antibiotics
   - Bactrin DS and Septra (both sulfa containing)
   - Augmentin (a penicillin)
   - Biaxen and Zithromax

   Cephalosporins (Keflex, ceclor, cedax, rocephin)
   Cipro, Levoquin, Avelox, Tequin

6. In some cases, topical steroid sprays (use after lavage and Ocean Spray)-

   - Flonase spray
   - Beconase spray
   - Nasonex

7. Mucolytics
   - Alkalol (used in lavage fluid)
   - Humabid-LA (Guaifenesin)
   - Organidin (contains iodide)
   - Saturated Solution Potassium Iodide (10% SSKI)

8. Multivalent flu vaccines if on steroids, DMARD's, significant heart or lung disease

(not recommended if history of adverse reactions to flu vaccines, the adjuvant in the vaccine or certain neurologic conditions)
an oral medication alternative to flu vaccine is amantadine, tamiflu or flumadine

TABLE 7: TREATMENT FOR SKIN AND MUCOUS MEMBRANE MANIFESTATION

Skin Creams*

Eucerin
Moisturel
Ticreme
Aquaderm
Complex 15
Neutrogena

Skin Lotions*

Keri lotion
Carmol
Lubriderm
Nutraderm
Lac Hydrin Five
Lacticare
Cetophile

Soaps and Shampoos*

Dove
Alpha Keri bar
Aveenobar

Topical Agents

gel
0.5% Hydrocortisone*
Lacticare HC (2.5% HC)
Neutrogena Sunblock
Mid-strength corticosteroids (Kenalog, Aristocort)--not for use on the face
Protoptic (Tacrolimus)

Anti-Candida for the Mouth

Lotrimin Cream*, external
Micatin cream*, external
Naftin cream, external
Spectazole cream, external
Loprox cream, external
Clortrimazole cream, external
Gynelotrimen cream*, external
Nystatin Oral Troche*
Mycelex troches*
Gynelotrimen vaginal suppositories*

Vaginal Lubricants and Anti-Candida*

Astroglide
Feminase
KY Jelly
Maxilube
Gyne-Moisture

Topical estrogens (postmenopausal)
Gynelotrimen vaginal suppositories or cream

Sunscreens

Coppertone Shade Spray Mist or Oil free

Any sunscreen greater than SPF 15 with UVA and UVB blockers such as

Solbar 50

TABLE 8: SYSTEMIC MEDICATIONS FOR TREATING AUTOIMMUNE DISEASES

Anti-Inflammatory

I. Tylenol (up to 4 per day)
II. Salicytes: Aspirin (enteric-coated 325 mg tabs preferred, and time release salicylates: Disalcid, Trilisate with less problems for GI bleeding.
(for cardiac protection, the dose is aspirin 85 mg per day) .

III. Nonsteroidal Anti-inflammatory agents (NSAIDs:) are divided into COX-1 and COX-2 drugs*

A. COX-1: probably more effective but also more GI problems in some patients.

many COX-1 are available over the counter:
Ibuprofen (Motrin, Advil, Nuprin) or Naproxen (Alleve)
and available as generics so less expensive
Sulinac (Clinoril) less renal side effect
Indocin (indomethacin)
Voltaren (diclofenac) (enteric-coated)
Lodine (ketoprofen) or Ansaid (flubiprofen) (studiessuggest decrease in periodontal disease)
Soon to go generic: Daypro (oxyprofen), Relafan (nambutone) (lower GI side effects)

*(most generic and over the counter NSAIDs are available as suppository or as a topical cream that is made up by compounding pharmacy which may help decrease gastric symptoms)

B. COX-2 anti-inflammatory drugs: more expensive, no generics, no more effective in pain control than COX-1 but lower rate of GI bleed in high risk patients
Celebrex 1 tab twice a day (caution if sulfa allergy)
Vioxx 25 mg per day
Valdecox 10 tab per day
*with COX-2 drugs, need to take low dose aspirin (81 mg) per day to maintain cardiac and stroke protection afforded by COX-1 drugs.

III. Cortisone and other Steroids
Prednisone, Medrol, Decadron)—very effective but side effects including increased oral yeast and periodontal disease in addition to diabetes, osteoporosis, glaucoma, hypertension, weight gain

IV. Drugs used to help modulate the immune response (more than just anti-inflammatory) but also may have side effects on different parts of the body.

A. Anti-malarial medications, since related compounds were first used to control symptoms of malaria although the current drugs are no longer used for control of infection.

Plaquenil (hydroxychloroquine)- dose based on weight (up to 8 mg/kg) and then very low retinal risk at this dose but should get eye check about 6 weeks after starting and then every 2-3 years for safety.(sooner if any new eye symptoms or change in vision)

Chloroquine is the "original antimalarial" but is not routinely used in US due to increased risk of eye toxicity; however, it is still used in many parts of the world (including Mexico and Japan) where hydroxychloroquine is not available

Quinacrine--used to be used in certain manifestations of Sjögren's including fatigue but no longer available from manufacturer and need to make sure no tendency for hemolytic anemia (i.e. G6PD deficiency)

B. Drugs Often Used in primarily in Rheumatoid Arthritis but also in Sjögren's and SLE

Methotrexate—weekly dosage is generally 7.5 to 15 mg (i.e. taken only one day per week) and useful for joint pains; can not be used if liver disease or hepatitis C. Uncommon side effect of lung disease, anemia and low white blood cell count

Arava (Leflunomide)- daily dosage, may have less lung toxicity than methotrexate

Imuran (azathioprine)—not widely used due to GI side effects in many patients but often used if associated autoimmune hepatitis.

C. Biologic Agents: Enbrel (etanercept) and Remicade (infliximab)—although may improve joint symptoms, in animal models they may increase risk for "lupus" like features; may reactivate tuberculosis in high risk patients, and may exacerbate multiple sclerosis

C. Drugs often used in Transplant recipients but also in some autoimmune patients

Cell Cept (mycophenolic acid). Although officially used in organ transplant recipients, it is also used in controlling immune problems.

Cyclosporin A (Sandimmune) and Rapamycin (Tacrolimus). Also drug generally used for transplant but sometimes used in other autoimmune disorders.

D. Drugs used in chemotherapy for cancer but in lower dose in patients with autoimmune problems

Cytoxan (cyclophosphamide)--generally given at monthly intervals by intravenous, although given orally on a daily basis in some cases.

Methotrexate is listed here as well as above, since it is officially listed as a chemotherapeutic agent and the listing as a chemotherapy causes frequent concern when patients read the drug insert.

Rituxian (rituximab). A monoclonal antibody given by intravenous infusion that is generally used in lymphoma but also in some intractable patients with autoimmune disease.

TABLE 9: DRUGS ASSOCIATED WITH DECREASED SALIVARY SECREATION AND INCREASED ORAL DRYNESS

I. Blood Pressure Medications
   A. a adrenergic-blockers (clonidine, catapress)
   B. beta adrenergic-blockers (Inderal, tenormin)
   C. Combined a,b -blockers (Labetolol)

II. Antidepressants (also used for neuropathy and other causes)
   A. Amitriptyline (Elavil)
   B. Nortriptyline (Pamelor)
   C. Desipramine
   D. Parnate, Nardil (MAO inhibitors)
   E. Mellaril (Dopamine blocker)

III. Muscle Spasm
   A. Flexeril
   B. Robaxin
   C. Baclofen

IV. Urologic Drugs
   A. Ditropan, Detrol
   B. Yohimbe

V. Cardiac
   A. Norpace

VI. Parkinson's
   A. Sinemet
   B. Requite

VII. Decongestants and Sleeping Aids (many are over the counter)
   A. Chlortrimeton
   B. Pseudofed (pseudoephredine)
   C. Atarax, Benadryl

TABLE 10: ICD-9-CM CODE ASSIGNMENTS FOR SJÖGREN'S SYNDROME, MANIFESTATIONS, SYMPTOMS AND RELATED DISORDERS

710.2	Sicca syndrome (Primary Sjögren's syndrome)
714.0	Rheumatoid Arthritis
710.0	Systemic Lupus Erythematous
710.1	Systemic sclerosis (scleroderma)
710.3	Dermatomyositis
710.4	Polymyositis
357.1	Polyneuropathy in collagen vascular disease
517.8	Lung involvement in diseases classified elsewhere
112.0	Candidiasis of mouth (thrush)
112.84	Candidial esophagitis
202.8	Lymphoma, malignant (non-Hodgkin's)
273.0	Polyclonal hypergammaglobulinemia
285.9	Anemia, unspecified
373.0x	Blepharitis, unspecified
443.0	Raynaud's syndrome
447.6	Arteritis, unspecified
521.0	Dental caries
523.4	Chronic periodontitis
530.81	Esophageal reflux
571.49	Other chronic (active) hepatitis
571.5	Cirrhosis of liver without alcohol (cryogenic)
571.6	Biliary cirrhosis
595.1	Chronic interstitial cystitis
135.3	Dyspareunia
729.1	Myalgia and Myositis, unspecified (Fibromyalgia)
375.15	Tear film insufficiency (Dry eye syndrome)
370.33	Keratoconjunctivitis sicca, not specified as Sjögren's [excludes (diagnosed) Sjögren's syndrome]
527.1	Hypertrophy of salivary glands
527.7	Disturbance of salivary secretion (Xerostomia)
719.4x	Pain in joint (requires fifth digit for site)
780.7	Malaise and fatigue
785.6	Enlargement of lymph nodes
797.2	Dysphagia
790.1	Elevated sedimentation rate

TABLE11 SPECIAL NEEDS OF THE SJÖGREN'S SYNDROME PATIENT AT THE TIME OF SURGERY

I. Preoperative Period
   A. Stop aspirin 1 week prior to surgery.
   B. Stop NSAIDs 3 days prior to surgery.
   C. Do not stop steroids.
   D. Notify anesthesiologist about specific problems with teeth, dentures, eyes, neck, sinuses, and lungs since this may affect the way intubation is performed.

II. Day of Surgery
   A. Take all medications with you to hospital in their bottles.
   B. Be sure to ask anesthesiologist to use an ocular ointment (such as Refresh PM) during surgery and in post-op recovery room.
   C. If receiving steroids, make sure these are taken on day of surgery either orally or through the IV. In some cases, a higher dose is required.
   D. All right to use artificial salivas (such as MouthKote) to keep mouth moist on the day of surgery when "NPO" (nothing per mouth).
   E. Ask anesthesiologist to use humidified oxygen in operating room and post-op.

III. Post-Operative Days
   A. Watch for yeast infections if receiving antibiotics.
   B. Use of artificial tears and salivas.
   C. Use of artificial salivas.

FIGURE LEGEND

Figure 1 The normal motion of the upper lid over the ocular surface is facilitated by a lubricating tear film.

Figure 2 In the dry eye patient, the tear film is inadequate and the increased friction as the upper lid moves over the globe is sensed by the patient as a painful, foreign body type sensation.

Figure 3 Rose Bengal is a vital dye that is used to rapidly and cheaply evaluate the ocular surface. A minute drop is placed under the lower lid and then immediately rinsed out with an artificial tear. Any areas of conjunctival irregularity briefly retain the Rose Bengal and can be visualized by eye or using a opthalmoscope. These areas of irregularity are better seen by the Ophthalmologist using a slit lamp, but significant keratoconjunctivitis sicca is visualized as demonstrated in this figure.

Figure 4: Schematic representation of normal regulation of tears and saliva. The ocular or oral surface receives signals from unmyelinated pain fibers that travel to certain regions of the central nervous system (called the lacrimatory or salvatory nuclei). These areas of the brain also receive input from the higher cortical centers and result in dryness (or secretion) in response to other factors such as stress, taste, odors or medications. The net signal is integrated in the lacrimatory or salvatgory nuclei and signals are sent back to blood vessels (by afferent nerves that use epinephrine as the transmitter) and to glands by efferent nerves that use acetylcholine as a neurotransmitter (called cholinergic nerves). The blood vessel serves as a soon of water (from plasma portion of blood) as well as nutrients and growth factors. The gland then adds additional proteins and pumps the secretion into the lacrimal or salivary gland tubules leading to ocular or oral surface (ie. tears or saliva).

Figure 5. Schematic representation of abnormalities in Sjögren's syndrome. The ocular surface again receives painful sensory input which it sends to the central nervous system. The salivatory and lacrimatory nuclei again send out efferent adrenergic and cholineric nerve fibers. However, lymphocytes which infiltrate the gland produce several different products which prevent the gland from fully responding to the signals. These include lymphocyte hormones called cytokines, autoantibodies that may block receptors for the neurotransmitter signals, and enzymes called metalloproteinases that interfere with optimal glandular function..

Figure 6: Photograph of salivary gland in Sjögren's syndrome. (A) Numerous lymphocytes are within the salivary gland. (B) A normal salivary gland that lacks lymphocytic infiltrates.

Figure 7

Figure 8

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